Recovery of menses after functional hypothalamic amenorrhoea: if, when and why

Pape, J ; Herbison, A E ; Leeners, B

Abstract: BACKGROUND Prolonged amenorrhoea occurs as a consequence of functional hypothalamic amenorrhoea (FHA) which is most often induced by weight loss, vigorous exercise or emotional stress. Unfortunately, removal of these triggers does not always result in the return of menses. The prevalence and conditions underlying the timing of return of menses vary strongly and some women report amenorrhoea several years after having achieved and maintained normal weight and/or energy balance. A better understanding of these factors would also allow improved counselling in the context of infertility. Although BMI, percentage body fat and hormonal parameters are known to be involved in the initiation of the menstrual cycle, their role in the physiology of return of menses is currently poorly understood. We summarise here the current knowledge on the epidemiology and physiology of return of menses. OBJECTIVE AND RATIONALE The aim of this review was to provide an overview of (i) factors determining the recovery of menses and its timing, (ii) how such factors may exert their physiological effects and (iii) whether there are useful therapeutic options to induce recovery. SEARCH METHODS We searched articles published in English, French or German language containing keywords related to return of menses after FHA published in PubMed between 1966 and February 2020. Manuscripts reporting data on either the epidemiology or the physiology of recovery of menses were included and bibliographies were reviewed for further relevant literature. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria served to assess quality of observational studies. OUTCOMES Few studies investigate return of menses and most of them have serious qualitative and methodological limitations. These include (i) the lack of precise definitions for FHA or resumption of menses, (ii) the use of short observation periods with unsatisfactory descriptions and (iii) the inclusion of poorly characterised small study groups. The comparison of studies is further hampered by very inhomogeneous study designs. Consequently, the exact prevalence of resumption of menses after FHA is unknown. Also, the timepoint of return of menses varies strongly and reliable prediction models are lacking. While weight, body fat and energy availability are associated with the return of menses, psychological factors also have a strong impact on the menstrual cycle and on behaviour known to increase the risk of FHA. Drug therapies with metreleptin or naltrexone might represent further opportunities to increase the chances of return of menses, but these require further evaluation.

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Recovery of menses after functional hypothalamic amenorrhea – if, when and why

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Abstract

BACKGROUND: Prolonged amenorrhea occurs as a consequence of functional hypothalamic amenorrhea (FHA) which is most often induced by weight loss, vigorous exercise or emotional stress. Unfortunately, removal of these triggers does not always result in the return of menses. The prevalence and conditions underlying the timing of return of menses vary strongly and some women report amenorrhea several years after having achieved and maintained normal weight and/or energy balance. A better understanding of these factors would also allow improved counselling in the context of infertility. Although body mass index (BMI), percentage body fat, and hormonal parameters are known to be involved in the initiation of the menstrual cycle, their role in the physiology of return of menses is currently poorly understood. We summarize here current knowledge on the epidemiology and physiology of return of menses.

OBJECTIVE AND RATIONALE: To provide an overview of (i) factors determining the recovery of menses and its timing, (ii) how such factors may exert their physiological effects, and (iii) whether there are useful therapeutic options to induce recovery.

SEARCH METHODS: We searched articles published in English, French or German language containing keywords related to return of menses after FHA published in PubMed between 1966 and December 2019. Manuscripts reporting data either on the epidemiology or on the physiology of recovery of menses were included and bibliographies were reviewed for further relevant literature. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria served to asses quality of observational studies.

OUTCOMES: Few studies investigate return of menses and most of them have serious qualitative and methodological limitations. These include (i) the lack of precise definitions for FHA or resumption of menses, (ii) the use of short observation periods with unsatisfactory descriptions, and (iii) the inclusion of poorly characterized small study groups. The comparison of studies is further hampered by very inhomogeneous study designs. Consequently, the exact prevalence of resumption of menses after FHA is unknown. Also, the timepoint of return of menses varies strongly and reliable prediction models are

lacking. While weight, body fat and energy availability are associated with the return of menses, psychological factors also have a strong impact on the menstrual cycle and behavior known to increase the risk for FHA. Drug therapies with metreleptin or naltrexone might represent further opportunities to increase chances for the return of menses, but require further evaluation.

WIDER IMPLICATIONS: Although knowledge on the physiology of return of menses is presently rudimentary, available data indicate the importance of BMI/ weight (gain), energy balance, and mental health. The physiological processes and genetics underlying the impact of these factors on the return of menses requires further research. Larger prospective studies are necessary to identify clinical parameters for accurate prediction of return of menses as well as reliable therapeutic options.

KEY WORDS: Recovery of menses; return of menses; restoration of the menstrual cycle; weight; BMI; percentage body weight; eating disorders; physical exercise; stress

Introduction

The human menstrual cycle is not only essential for reproduction but also for general well-being (Walf and Frye 2006). Estradiol is needed for adequate bone, cardiovascular, mental, and vaginal health (Levin, Jiang, and Kagan 2018; Iorga et al. 2017; Manonai, Chittacharoen, and Theppisai 2004; Rettberg, Yao, and Brinton 2014; Filova et al. 2015; Gordon et al. 2017). Weight loss, eating disorders, exercise, and emotional stressors suppress the activity of the GnRH neuronal network and to produce functional hypothalamic amenorrhea (FHA) (Drew 1961; Mecklenburg et al. 1974; Gadpaille, Sanborn, and Wagner 1987; Berga and Girton 1989; Fries, Nillius, and Pettersson 1974; Frisch and McArthur 1974; Pirke et al. 1989; Warren et al. 1999; Sanchez-Garrido and Tena-Sempere 2013; Roa et al. 2010; Castellano and Tena-Sempere 2016; Garcia-Garcia 2012; Berga and Naftolin 2012; Bullen et al. 1985; Loucks et al. 1989). A reduction in GnRH drive results in abnormal LH pulse frequency generating cycle disturbances (Berga and Girton 1989; Laughlin, Dominguez, and Yen 1998; Ackerman et al. 2012). By definition, FHA is only diagnosed after anatomic or organic causes of amenorrhea have been excluded.

FHA is responsible for 20–35% of secondary amenorrhea (American Society for Reproductive Medicine 2008). It occurs in up to 89% of women with anorexia nervosa and up to 60% of high-performance athletes (Andersen and Ryan 2009; Watson and Andersen 2003; Roupas and Georgopoulos 2011; Sanborn, Martin, and Wagner 1982; Warren and Perlroth 2001). Because of pre-existing cycle irregularities, the concept of post-pill amenorrhea was abandoned in the early 80ies (Barnhart and Schreiber 2009; Jacobs et al. 1977); 97% of women experience return of menses within a median time of 32 days after discontinuation of combined oral contraceptives (Davis et al. 2008).

FHA is currently treated symptomatically by hormonal replacement therapy to prevent unfavourable health consequences resulting from a lack of estrogens. However, hormone therapy may be associated with an increased risk for breast cancer, venous thromboembolism or stroke (Marjoribanks et al. 2017; Magliano et al. 2006; Collaborative Group 2019). Infertility in FHA women is presently treated with timed

intercourse, intrauterine inseminations or IVF/ICSI and, while highly effective, the latter are costly, time-consuming, and burdensome (Katz et al. 2011).

To improve counselling and provide guidance for future research, this review summarizes available knowledge on the factors allowing the return of menses. While focussed primarily on clinical data, we also include a review of the mechanistic and translational aspects of anovulation and the return of menses gained from animal studies. We evaluate (i) which factors determine the recovery of menses and its timing, (ii) how these factors exert their physiological effects, and (iii) whether there are any useful therapeutic options to induce recovery.

Method

A systematic review of epidemiological data on resumption of menses in humans was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria (Liberati et al. 2009). A PubMed search from 1966 to February 2020 included the MeSH terms: “re-onset/ return or recovery of menses/menstruation”, “anovulation”, “amenorrhea”, combined with, “hypothalamus”, “pituitary”, “gonadotropin releasing hormone (GnRH)”, “GnRH pulse generator”, “leptin”, “ghrelin”, “glucose”, “insulin”, “cortisol”, “kisspeptin” AND/ OR “influencing factors”, “body weight”, “energy balance”, “eating disorders”, “nutrition”, “diet”, “sports”, “stress”, “mental health”, “posttraumatic stress disorder (PTSD)”, “genetics” and/or “treatment”, “medication”, “stress management”, “psychotherapy”, “cognitive behavioural therapy (CBT)”. A “return of menses” set element AND/ OR a “factor/ physiology” set element were always included in title, abstract or all fields, where capital letters indicate Boolean connectors. All studies were screened by title and abstract. Eligible articles in English, German and French were read, and the relevant information was extracted. Secondary literature from these studies was evaluated for further relevant publications.

FHA is considered to be chronic anovulation not due to any identifiable anatomic or organic causes, i.e. it is a diagnosis of exclusion without any generally accepted diagnostic criteria (Bomba et al. 2007; Gordon 2010; Gordon et al. 2017; Genazzani et al. 2010; Sowinska-Przepiera et al. 2015). The differential diagnosis between amenorrhea and FHA please has recently been reviewed (Gordon et al. 2017). Polycystic ovary syndrome (PCOS) was considered a diagnosable cause of amenorrhea and therefore not included within the present review.

Any study reporting at least one menstruation after a phase of FHA was considered within this review. The initial systematic search yielded a total of 1424 manuscripts published between 1966 and February 2020, with forty-nine manuscripts directly addressing either recovery of menses (N = 34) or prolonged amenorrhea (N = 15) in humans. Prospective (N = 23) and cross-sectional studies (N = 13) investigating between 12 and 463 participants formed the majority of research. In addition, five retrospective, six case-control studies and two case reports were analysed.

Quality of observational studies was assessed using the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) criteria (von Elm et al. 2007). Case reports were evaluated by the Consensus-based Clinical Case Reporting Guideline Development (CARE) Guidelines (Gagnier et al. 2013).

Animal studies investigating the neural mechanisms underlying the impact of metabolic factors on the reproductive axis were considered by AEH. To ensure, no major paper was omitted, recent reviews on the subject from three different research groups were consulted (Ronnekleiv, Qiu, and Kelly 2019; Vazquez, Velasco, and Tena-Sempere 2019; Chianese et al. 2018; Evans and Anderson 2017).

Methodological details of included studies

Resumption of menses and/or risk factors for prolonged amenorrhea were investigated predominantly after the treatment of eating disorders (N = 29), but also in athletes (N = 13) or in stress-related FHA (N = 7). Most studies compared anthropometric data (body weight, BMI, body fat) or hormonal parameters between women with and without return of menses aged < 30 years. Out of the 34 studies directly

investigating the recovery of menses, twelve controlled for well-known hormonal causes of cycle disturbances and related diseases such as PCOS, thyroid diseases, hyperprolactinemia, adrenogenital syndrome, disturbances of the adrenal and pituitary gland or premature ovarian insufficiency. The underlying pathophysiology and the timeline of recovery of menses was rarely addressed. Of the 47 observational studies, 13 were of low, 29 of medium, and 5 of high quality (von Elm et al. 2007). The quality of case reports was middle (Kopp-Woodroffe et al. 1999) to high (Mallinson et al. 2013).

Results

We first define the diagnostic criteria for FHA and the resumption of menses before summarizing the causes of FHA, as their reversal may play a role in the return of menses. We next address potential physical and psychological mechanisms involved in the onset and end of FHA including their interactions. Finally, we will give an overview of currently available treatment options.

Diagnosis of functional hypothalamic amenorrhea (FHA)

To diagnose FAH, 16 studies relied solely on self-reported amenorrhea (Table 1) while 30 studies evaluated initial cycle status by serum (estradiol, FSH and LH) or urine (estrone glucuronide, pregnanediol glucuronide and LH) hormonal parameters. Transvaginal ultrasound of the ovaries was performed in four studies and radiography of the sella turcica in one (Falsetti et al. 2002). A positive response to a GnRH stimulation test was another diagnostic criterion (Pentz and Nakic Rados 2017). FHA was diagnosed after at least three (16 studies) or six (8 studies) months of amenorrhea. Further prerequisites for the diagnosis of FHA were regular menses prior to FHA (Sterling et al. 2009; Christo et al. 2008) or a coincidence of amenorrhea with increased exercise or low weight (Welt et al. 2004). Four studies provided no specific definition of FHA (Bodell and Mayer 2011; Chou et al. 2011; Holtkamp et al. 2003; Rigaud et al. 2011).

Diagnostic criteria for resumption of menses

193 The majority of studies (N = 24) did not provide any definition of resumption of menses (Table 1). Of the
194 34 studies explicitly addressing resumption of menses, 31 relied on self-reported bleeding with 12
195 differentiating between one, two or three consecutive spontaneous menstrual cycles as cut-off to
196 diagnose recovery of menses. Four studies required a cycle length of less than 36 days to diagnose
197 recurrence of menses. Further criteria were the exclusion of other potential causes of vaginal bleeding
198 such as infection or trauma. Six studies evaluated either with urine / serum hormonal parameters or by
199 ultrasound whether menstrual cycles were ovulatory.
200
201 **Body weight, energy availability and return of menses**
202 The association between body weight/ energy availability and return of menses was explored in eating
203 disorders, or in the context of physical activity (Table 2 and 3, Fig. 1). The majority of the 19 studies
204 support that anthropometric characteristics i.e. BMI, body weight or body composition are associated
205 with resumption of menses (Table 2). However, there are also opposite results (Arimura et al. 2010; El
206 Ghoch et al. 2016).
207
208 *Eating disorders, body weight and energy availability*
209 Patients who resume menses after eating disorders have a higher BMI (19 kg/m^2 vs 17.5 kg/m^2) or body
210 weight than those who do not (Dempfle et al. 2013; Le Grange et al. 2012). As with individual differences
211 at the onset of amenorrhea, the individual BMI for recovery of menses differs strongly and comparison of
212 different studies is hampered by the use of different weight measures. For example, two-thirds of
213 anorectic girls became amenorrheic at a BMI between 17 and 18.9 kg/m^2 while the remaining third had a
214 normal BMI (Berner et al. 2017). A higher BMI at the onset of amenorrhea is associated with a higher BMI
215 needed to allow return of menses (Berner et al. 2017; Pitts et al. 2014). At or above a BMI of 19 kg/m^2
216 and $\geq$ 23% body fat, about 50% of women are expected to resume menses (Tinahones et al. 2005). Women
217 with a BMI of 14 kg/m^2 and 11% body fat still had a probability of 25% for recovery of menses (Winkler et

al. 2017). Generally, recovery of menses seems to require about 2kg more than the weight of the woman at the time at which menses were lost (Golden et al. 1997).

Using other weight parameters, menstrual recovery was reported to occur at 91.6 ± 9.1% of standard body weight (median body weight adjusted for age, gender, frame size and height) (Frisancho 1984) of (Golden et al. 1997) or 94.9 ± 9.3% of expected body weight (EBW = optimal weight related to height and/or age for healthy nutritional status with the lowest rate of mortality) (Faust et al. 2013). In anorectic postmenarcheal girls, a BMI $\geq 27^{th}$ percentile based on percentiles derived from different national health surveys or a BMI at the 24^{th} percentile based on BMI measurements from 17 German studies, seems to be necessary for recovery of menses (Dempfle et al. 2013; Golden et al. 2008; Kuczmarski et al. 2000). Interestingly, during spring or summer, anorectic women needed on average 2 kg less for resumption of menses than during fall or winter (Favaro and Santonastaso 2009).

According to prospective data from anorectic patients, the onset and regularity of menstrual cycles requires between 18% and 28% of body fat (El Ghoch et al. 2016; Frisch and McArthur 1974; Frisch 1987; Karountzos et al. 2017; Misra et al. 2006; Tokatly Latzer et al. 2019; Winkler et al. 2017; Pitts et al. 2014) (Table 2). However, even with 36% body fat, not all women resumed menses (Tinahones et al. 2005). An increase of about 1% in total body fat at discharge after anorexia treatment was reported to augment the probability of menses by approximately 14% per year (El Ghoch et al. 2016). Modifications in fat distribution following weight recovery seem to be irrelevant for resumption of menses (Dei et al. 2008; Mayer et al. 2009).

Independent from absolute weight, dieting is considered to be a risk factor for amenorrhea (Martini et al. 2016). After at least one year of stable normal weight, caloric intake still differed significantly between women with persisting FHA and age-, weight-, as well as body fat- matched control women with a regular cycle (Miller et al. 1998). In addition, eating disorders are closely associated with stress (Smith et al. 2018;

243 Keski-Rahkonen and Mustelin 2016), which may further increase the risk for prolonged amenorrhea (see
244 below).
245 A few studies have reported no significant association between body fat and the return of menses
246 (Arimura et al. 2010; Golden et al. 1997; Dei et al. 2008; Jacoangeli et al. 2006). Arimura and colleagues
247 (Arimura et al. 2010) reported no resumption of menses immediately after weight recovery but this may
248 have been too short a period of observation as studies supporting an association are based on a longer
249 follow-up period (El Ghoch et al. 2016; Misra et al. 2006; Karountzos et al. 2017; Pitts et al. 2014; Tokatly
250 Latzer et al. 2019). Golden and co-workers (Golden et al. 1997) applied skinfold thickness measurements,
251 which are of rather limited diagnostic quality to evaluate body fat (El Ghoch et al. 2012). The cross-
252 sectional studies reporting no association were either small (Jacoangeli et al. 2006) or applied an arbitrary
253 definition of weight recovery (Dei et al. 2008).
254 In summary, the absolute BMI has to be between 17.7±1.4 kg/m^2 (Pitts et al. 2014) and 22.9±2.5
255 kg/m^2 (Cialdella-Kam et al. 2014) and body fat between 18% and 28% to allow resumption of menses. The
256 BMI at occurrence of amenorrhea is important in setting the individual weight target for recovery of
257 menses. As current research on the association between eating disorders has focused on weight,
258 information is lacking on whether specific eating disorder-related malnutrition is related to amenorrhea.
259
260 Prognosis and timing of return of menses after weight recovery: Between 35% and 54% of women
261 experience return of menses immediately after achieving normal weight (Arimura et al. 2010; Dempfle et
262 al. 2013; El Ghoch et al. 2016; Winkler et al. 2017; Bodell and Mayer 2011). After a longer
263 treatment/observation period, these rates may rise to 80% or even 100% (Golden et al. 1997; Kohmura
264 et al. 1986; Jacoangeli et al. 2006; Tinahones et al. 2005) (Table 3). Studies providing exact information
265 on the time to recovery of menses after weight restoration reported a broad range from 50 ± 33 days up
266 to 14 ± 12 months until the return of menses (Arimura et al. 2010; Faust et al. 2013; Golden et al. 1997;
267 Karountzos et al. 2017; Swenne 2004; Tinahones et al. 2005; Tokatly Latzer et al. 2019).

Between 5% and 68% of women have been reported to remain amenorrheic after weight recovery (Dempfle et al. 2013; El Ghoch et al. 2016; Golden et al. 1997; Karountzos et al. 2017; Jacoangeli et al. 2006; Tokatly Latzer et al. 2019; Favaro and Santonastaso 2009; Misra et al. 2006; Pitts et al. 2014; Kohmura et al. 1986) with between 5% and 14% ultimately remaining amenorrheic (Golden et al. 1997; Jacoangeli et al. 2006).

According to the guidelines of the Endocrine Society, "the term "functional" hypothalamic amenorrhea implies that correction or amelioration of the causal factors will restore ovulatory ovarian function" (Gordon et al. 2017). However, the return of menses does not necessarily occur after such correction. In previously anorectic adolescents, 86% experienced the return of menses within six months of stable weight (Jacoangeli et al. 2006). After one year of successful treatment against anorexia, 35% - 68% of women resumed menses and 95% had recovered by year two (Dempfle et al. 2013; El Ghoch et al. 2016; Golden et al. 1997; Golden et al. 2008; Abbate Daga et al. 2012; Bodell and Mayer 2011; Faust et al. 2013; Misra et al. 2006). As all adolescents with premenarchal onset of anorexia remained amenorrheic at the 12-month follow-up following weight restoration, the premenarchal onset of eating disorders seems to be an unfavourable factor for recovery of menses (Dempfle et al. 2013). About 5% of previously anorectic adolescents remain amenorrheic two years after achieving normal weight (Golden et al. 1997). In the study with the longest observation period of 13 years, 97% of anorectic women resumed their menses (Rigaud et al. 2011). In that study, a BMI >18.5 kg/m^2 and lack of physical hyperactivity explained 67% of the variance in return of menses.

Although return of menses clearly depends on prerequisites such as BMI or energy availability, individual recovery is difficult to predict. None of the available mathematical models succeed in predicting the exact time for return of menses. Percent body fat and BMI have equal predictive quality but explain only 14% of the variation in recovery of menses (Winkler et al. 2017).

Excessive exercise, body weight and energy availability

Total absolute and percentage weight gain, as well as BMI, are found to differ between athletes with and without recovery of menses (Arends et al. 2012). Nutrition and energy balance also play a role in the return of menses; amenorrheic athletes eat less fat but more carbohydrates and fiber than those with a normal menstrual cycle (Laughlin, Dominguez, and Yen 1998; Cialdella-Kam et al. 2014). Energy availability (defined as the net input of energy remaining after exercise training and energy needed for all other metabolic processes, normalized to kg of lean body mass (Loucks and Thuma 2003)) is lower in amenorrheic than in eumenorrheic exercising women (Williams et al. 2001), but does not differentiate between ovulatory and anovulatory cycles (Reed et al. 2015). Athletes with amenorrhea often consume too few calories for their energy needs (Melin et al. 2016; Elliott-Sale et al. 2018) and the likelihood of exercise-related menstrual abnormalities seems to vary with the magnitude of the energy deficit (Williams et al. 2015). LH pulsatility has been reported to be disrupted when energy intake in women is less than 30 kcal/kg lean body weight per day (Loucks and Thuma 2003; Loucks, Kiens, and Wright 2011; Dueck et al. 1996; Reed et al. 2015). Also, an overall reduction of energy by 470 and 810 kcal per day in women with an initial body fat between 15–35% and a BMI 18–25 kg/m^2 increases the risk for menstrual cycle disturbances (Williams et al. 2015). Menstrual function may already stop at energy availabilities above this threshold, but specific causes for these differences have not be identified as yet (Lieberman et al. 2018; Reed et al. 2015; Holtzman and Ackerman 2019). It is possible that age-related physiological differences during adolescence may influence actual parameter thresholds. However, very few studies have so far addressed the identification of clear cut-off values and related influencing factors. Unfortunately, the exact extent of physical activity and details of nutrition and nutritional supplements are only assessed in a few studies, which makes comparison of results difficult.

Athletes with FHA also show a significantly lower resting energy expenditure compared to eumenorrheic athletes, but part of this difference may result from discrepancies in initial and actual body weight or BMI between study participants (Sterling et al. 2009; Christo et al. 2008).

318 Prognosis and timing of the return of menses after adjusting energy and weight: Weight gain or increased
319 energy availability by nutritional supplements, and a decrease in energy expenditure, increases the
320 chances for resumption of menses (Table 3) (Arends et al. 2012; Cialdella-Kam et al. 2014; Kopp-
321 Woodroffe et al. 1999; Lagowska et al. 2014; Mallinson et al. 2013). In athletes close to normal weight,
322 amenorrhea may reverse when training is reduced (Benson, Engelbert-Fenton, and Eisenman 1996;
323 Warren 1980). With adequate calorie-intake, menses are expected to reoccur in 75% – 100% of women
324 (Kopp-Woodroffe et al. 1999; Mallinson et al. 2013; Cialdella-Kam et al. 2014). An appropriately balanced
325 diet with the simultaneous limitation of training volume and intensity is therefore the main tool to reduce
326 menstrual disorders in athletes (Nattiv et al. 2007; Manore, Kam, and Loucks 2007) with percent weight
327 gain being a significant positive predictor for recovery of menses (Cialdella-Kam et al. 2014).
328 After adjusting weight and energy balance, the time until recovery of menses varied from 11 weeks to 33
329 months (Arends et al. 2012; Cialdella-Kam et al. 2014; Kopp-Woodroffe et al. 1999; Mallinson et al. 2013).
330 While one study showed a correlation between the duration of amenorrhea and recovery of menses
331 (Cialdella-Kam et al. 2014), another study did not support such association (Arends et al. 2012).
332
333 *Comparison of women with eating disorders to women with excessive exercise*
334 The relevance of different factors involved in the resumption of menses seems to vary in relation to
335 factors involved in the initiation of amenorrhea. In eating disorders, the extent of weight and/or fat gain
336 seems to be particularly important for recovery (El Ghoch et al. 2016; Dempfle et al. 2013) whereas in
337 normal-weight athletes, adequate energy intake seems to play the major role (Reed et al. 2015). Women
338 with eating disorders show addictive and obsessive-compulsive traits, that can manifest in excessive
339 physical activity (Davis and Claridge 1998). Amenorrhea is more prevalent among athletes with eating
340 disorders (Peric et al. 2016), and 39%–48% of women with eating disorders also engage in excessive
341 exercise, i.e. there is a common overlap of risk factors for prolonged amenorrhea (Freimuth, Moniz, and
342 Kim 2011).
343

Potential mechanisms underlying the return of menses

Body weight and energy availability

There is a well-documented regulatory influence of energy balance on fertility. For the most part this is brought about by circulating energy-related hormones and metabolites that modulate the functioning of central hypothalamic networks controlling the secretion of gonadotropin-releasing hormone (GnRH). Mammalian fertility is governed by a neural network that integrates a range of internal and external cues to control the release of GnRH that, in turn, generates pulsatile and surge profiles of gonadotropin secretion (Fig. 2) (Herbison 2016). Although pulsatile gonadotropin secretion occurs throughout the menstrual cycle, the frequency and amplitude of pulses change across the cycle to ensure the correct maturation of developing follicles (Herbison 2018). Studies in animal models have now demonstrated that a population of kisspeptin neurons located in the hypothalamic arcuate/infundibular nucleus operate as the "GnRH pulse generator" by activating the GnRH neurons to generate pulsatile gonadotropin secretion (Herbison 2018; Plant 2019). It is clear from both animal and human studies that chronic and acute energetic stressors can result in a marked reduction in LH pulsatility (Loucks, Verdun, and Heath 1998; Hilton and Loucks 2000; Wade and Jones 2004; Loucks and Thuma 2003). In addition to pulses, the hypothalamus and pituitary generate the mid-cycle LH surge that initiates ovulation. Disturbances of either pulsatile or surge profiles of gonadotropin hormone secretion can suppress fertility.

Investigators have now discovered a wide range of circulating factors that inform the brain on the metabolic and energy status of the body. Whilst these hormones are primarily driving appropriate central energy regulation through appetite and energy expenditure, the same signals are thought to be used to regulate the GnRH neuron network and, accordingly, the menstrual cycle (Evans and Anderson 2017; Fernandez-Fernandez et al. 2006; Navarro and Kaiser 2013). Discussed below are the roles of leptin, ghrelin and insulin, considered to be the primary peripheral factors signalling information on body weight and energy availability to the GnRH neuron network. The impact of activating stress pathways, often not easily separated from the energy deficit itself, is also considered.

The vast majority of work in this field has examined how energy insufficiency/stress operates to suppress pulsatile gonadotropin secretion resulting in cycle abnormalities and infertility. Unfortunately, very little work has examined the return of fertility with the presumption being that it is a reversal of the mechanism that initiates the infertility generated by energy stress. Perhaps surprisingly, the resumption of pulsatile LH secretion in re-fed, acutely energetically-stressed women is much slower (taking up to one week) than in men or in experimental animals examined to date (Loucks, Verdun, and Heath 1998; Cameron 1996; Szymanski et al. 2007).

Leptin: Secreted by adipocytes into the circulation, leptin signals body fat stores with elevated levels acting on the hypothalamus to reduce feeding and increase energy expenditure. Leptin concentrations also fluctuate on a shorter time scale unrelated to weight or body fat, being reduced with fasting (Ahima et al. 1996; Flier 1998; Grinspoon et al. 1997). Women with anorexia and exercise-induced amenorrhea are hypoleptinemic (Audi et al. 1998; Jimerson et al. 2000; Mantzoros et al. 1997; Miller et al. 1998). Interestingly, even after controlling for body fat, women with exercise- or eating-related FHA have significantly lower leptin levels than those of their ovulatory counterparts (Miller et al. 1998; Warren et al. 1999; Andrico et al. 2002). A leptin level of 1.85 ng/ml (Reference 4.1 – 25 ng/ml) appears to be the critical level for amenorrhea (Kopp et al. 1997). Values above this lead to an increase of LH (Holtkamp et al. 2003) and more than 20% of amenorrheic women recover menses at levels > 1.85 ng/ml (Tinahones et al. 2005). However, a cross-sectional study found no differences in leptin levels or BMI between two groups of anorectic patients with and without amenorrhea (Audi et al. 1998). Furthermore, the reinstatement of pulsatile LH secretion by refeeding chronically food-restricted ewes was found to be unrelated to circulating leptin concentrations (Nakamura, Osonoi, and Terauchi 2010).

The mechanisms through which leptin controls fertility are multifaceted and may involve peripheral as well as central actions. For example, high leptin levels enhance oocyte nuclear and cytoplasmic maturation and affect follicle rupture and corpus luteum formation (Craig et al. 2004; Ruiz-Cortes et al.

2003). However, studies in rodents indicate that the primary impact of leptin on fertility likely arises through central mechanisms. The deletion of leptin receptors from just the brain results in infertility (Quennell et al., 2009) and actively blocking leptin signalling in the brain reduces pulsatile LH secretion (Carro et al., 1997). These effects are often considered to be permissive in the sense that they enable normal functioning of the GnRH neuron network rather than actually determining its magnitude or mode of action.

Many studies in animal models have tried to establish the neural pathway through which leptin influences GnRH neurons. As GnRH and kisspeptin neurons seem unlikely to express functionally significant leptin receptors themselves, attention has focussed upon indirect mechanisms by which circulating leptin modulates the activity of neurons that project to and control the kisspeptin and/or GnRH neurons (Evans and Anderson 2017; Navarro and Kaiser 2013). While roles have been proposed for leptin to operate through premammilary nucleus neurons (Donato et al. 2011) and GABA neurons in the brain (Zuure et al. 2013) to control GnRH secretion, most evidence favours an effect of leptin on neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons (Ronnekleiv, Qiu, and Kelly 2019). These are the same cells implicated in the potent actions of leptin on energy metabolism. As such, it is envisaged that low leptin levels act through NPY/AgRP neurons to both increase feeding and disable the normal menstrual/estrous cycle. Precisely how the leptin-sensing NPY/AgRP neurons impact upon GnRH secretion remains unclear with the most likely pathway being through direct the control of the kisspeptin neuron pulse generator (Hessler, Liu, and Herbison 2020). The resumption of menses in FHA woman may result from the re-establishment of normal energy balance leading to normalised leptin levels and consequently reduced NPY/AgRP neuron activity permitting normal pulsatile GnRH secretion.

Insulin & glucose: Diet and negative energy balance associated with FHA generate a hypometabolic state that includes, among other abnormalities, lowered circulating insulin levels (Laughlin and Yen 1996). As such, insulin is one potential pathway through which the menstrual cyclicity is regulated in women with exercise- or diet-related FHA. Indeed, fasting insulin levels are higher in women with a history of eating

disorders after return of menses compared to women remaining amenorrheic (Dei et al. 2008; Karountzos et al. 2017; Tinahones et al. 2005). A similar association has been confirmed following weight-recovery (defined as an increase in weight >85% of the initial weight before amenorrhea) (Dei et al. 2008), during the 8 - 26 months treatment phase for an eating disorder (Karountzos et al. 2017) and in the early follicular phase in women with resumption of menses (Tinahones et al. 2005). However, studies in male monkeys indicate that the key factor underlying the return of normal LH pulsatility following a nutritional stress is the increase in caloric intake independent of glucose or insulin (Cameron 1996).

It is likely that insulin operates at multiple levels of the reproductive axis to exert a modulatory effect upon fertility. Unlike leptin, there is much less certainty that insulin actions in the brain are necessary or critical. Whereas an early study reported that the deletion of insulin receptors selectively from the brain of mice resulted in mild hypogonadism (Bruning et al. 2000), another study found no reproductive abnormalities (Evans and Anderson 2017). Further, the deletion of insulin receptors selectively from GnRH or kisspeptin neurons, or a range of other neuronal phenotypes, has been found to have no impact upon fertility in mice (Qiu et al. 2013; Divall et al. 2010; Evans and Anderson 2017). Interestingly, over nutrition resulting in obesity-induced infertility in mice appears to be dependent, at least in part, upon insulin signalling at the GnRH neuron (Divall et al. 2010), pituitary gland (Brothers et al. 2010) and ovary (Wu et al. 2012). It is unknown whether this represents a similar mechanism to the cycle disturbances resulting from energy deficit.

Glucose concentrations themselves may represent an independent pathway through which energy stress suppresses the menstrual cycle. For example, reducing glucose availability within the brain suppresses pulsatile LH secretion in experimental animals (Murahashi et al. 1996; Lado-Abeal et al. 2002) and binge eating or binge-purge behaviour in humans is associated with a higher risk for FHA (Johnson and Whitaker 1992). Differentiating any role of glucose from insulin in energy stress-evoked FHA can be challenging, but available evidence is equivocal regarding whether glucose may be more or less important than alterations in insulin secretion (Roland and Moenter 2011; Szymanski et al. 2007; Cameron 1996). Precisely where glucose acts to modulate the menstrual cycle remains unclear given the ubiquitous requirement for

glucose and multiple different sensors that could be involved. Peripherally, glucose deficiency can compromise the ability of the oocyte to reach the second metaphase, to extrude the first polar body (Dominko and First 1997), and to achieve the blastocyte stage (Dan-Goor et al. 1997). There is also evidence demonstrating that glucose modulates the electrical excitability of GnRH neurons in a direct manner through AMPkinase, as well as indirectly through glucose-sensitive inputs from neurons located in the brainstem (Roland and Moenter 2011). Thus, the return of a normoglycemic state to women with FHA may contribute to the return of menses through direct glucose actions at multiple and varied sites throughout the reproductive axis.

Ghrelin: Ghrelin acts as a signal of starvation and energy insufficiency and is secreted by the stomach in a fluctuating pattern with elevated concentrations occurring prior to meals (Tena-Sempere 2013). Unsurprisingly then, ghrelin concentrations are found to be continuously elevated in women suffering from chronic undernutrition and exercise-induced amenorrhea (De Souza et al. 2004; Schneider, Monaco, and Warren 2008; Tolle et al. 2003; Christo et al. 2008). In this case, an energy deficient state results in elevated ghrelin levels (compared with *reduced* leptin, insulin and glucose concentrations) and evidence indicates that elevated ghrelin levels suppress gonadotropin secretion (Kluge et al. 2012). Hence, the elevated ghrelin levels found in women with FHA may represent another pathway contributing to their suppressed fertility (Christo et al. 2008).

In common with the other potential hormonal mediators highlighted above, ghrelin has multiple potential sites of action within the reproductive axis. Ghrelin receptors (GHS-R) are widely expressed in the ovary, pituitary and within the regions of the hypothalamus involved in the control of GnRH secretion (Gaytan et al. 2003; Gaytan et al. 2005; Tena-Sempere 2007). However, animal studies indicate that ghrelin signalling is not itself essential for the suppression of cycles as the deletion of the ghrelin receptor in mice has no impact on fertility or feeding (Sun, Ahmed, and Smith 2003). It does, however, appear to modulate glucose sensing, insulin sensitivity and the stress response (Sun et al. 2008; Sominsky et al. 2017) and may, through these mechanisms, have some role in indirectly modulating the menstrual/estrous cycle (Evans

474 and Anderson 2017).

475

476 Other hormones: While the discussion above considers what are thought to be the primary hormonal
477 signals modulating fertility, women with energy-related FHA exhibit multiple other endocrine
478 abnormalities. For example, FT3, FT4, and TSH are commonly decreased in amenorrheic women with
479 eating disorders and increase after resumption of menses (Dei et al. 2008; Karountzos et al. 2017;
480 Tinahones et al. 2005). Whether and how thyroid hormones are related to the resumption of menses
481 remains unclear. Similarly, levels of growth hormone and insulin-growth factor-1 (IGF1) are reduced in
482 FHA (Bomba et al. 2007; Miller et al. 2004). An IGF-1 level of >342.8 ng/ml has been proposed to be a
483 predictor for return of menses (Cominato et al. 2014), although two other studies have found no positive
484 correlation (Falsetti et al. 2002; Arimura et al. 2010).

485

486 *Psychological and psychogenic factors*

487 The hypothalamic neurons regulating GnRH pulses not only respond to metabolic conditions but also to
488 psychological and psychogenic factors (Drew 1961; Mecklenburg et al. 1974; Gadpaille, Sanborn, and
489 Wagner 1987; Berga and Girton 1989; Fries, Nillius, and Pettersson 1974; Frisch and McArthur 1974; Pirke
490 et al. 1989; Warren et al. 1999; Sanchez-Garrido and Tena-Sempere 2013; Roa et al. 2010; Castellano and
491 Tena-Sempere 2016; Garcia-Garcia 2012; Berga and Naftolin 2012; Bullen et al. 1985; Loucks et al. 1989).
492 Emotional stressors as measured by both subjective and objective parameters increase the risk for FHA in
493 humans and in animals (Sanders and Bruce 1999; Gordley et al. 2000; Bomba et al. 2007; Brown et al.
494 1983; Kondoh et al. 2001; Facchinetti et al. 1993; Harlow and Matanoski 1991). In adolescent girls,
495 changing school, initiating sexual activity, breaking up with a boyfriend, chronic illness, death of a friend
496 or family member, and family conflicts may result in FHA (Bomba et al. 2007). Psychological risk factors
497 that chronically activate the HPA axis include perfectionism, high need for social approval, conditional
498 love and/ or unrealistic expectations of self and others (Berga and Girton 1989; Giles and Berga 1993;
499 Marcus, Loucks, and Berga 2001). College students who later became amenorrheic have been reported

to be more anxious, stubborn, and perfectionist (Shanan et al. 1965). It is possible that sleep deprivation may exacerbate this by further activating the HPA axis to induce anovulation and amenorrhea (Lateef and Akintubosun 2020). These effects are also seen in monkey models where a change of social environment, or disruptive social interactions with group members can generate amenorrhea (Michopoulos et al. 2009; Bethea, Centeno, and Cameron 2008; Bethea et al. 2005; Wagenmaker et al. 2009; Adams, Kaplan, and Koritnik 1985).

Traumatic events such as sexual assault, incarceration or natural disasters may induce post-traumatic stress disorders (PTSD) (Beaglehole et al. 2018; Leeners et al. 2007), which is another risk factor for FHA (Berga and Girton 1989). For example, FHA has been reported after floods (Neuberg et al. 1999) and in women interned in a concentration camp during the Second World War before any malnutrition became evident (Sydenham 1946). Incarcerated women show a higher prevalence of amenorrhea, with women reporting additional stress factors such as childhood physical or sexual abuse, economic deprivation or coming from a racial and ethnic minority being at increased risk (Allsworth et al. 2007).

It is also evident that behaviours such as over-exercise or restricting eating may reflect an underlying mental or psychiatric disease (Giles and Berga 1993; Marcus, Loucks, and Berga 2001; Berga 2008). For instance, amenorrheic runners were found to suffer significantly more often from major affective or eating disorders than menstruating runners (Gadpaille, Sanborn, and Wagner 1987). Also women with anxiety disorders or depression have been found to be at increased risk for FHA (Fava et al. 1984; Joffe et al. 2006; Lawson et al. 2009).

Women with FHA often display combinations of psychological factors that can activate stress responses, induce metabolic disturbances, and/or result in excessive exercising (Marcus, Loucks, and Berga 2001; Giles and Berga 1993; Faust et al. 2013). In rhesus monkeys, the combination of low-level psychosocial stress and moderate energy imbalance resulted in a higher proportion of abnormally long or anovulatory cycles than either stressor alone (Williams, Berga, and Cameron 2007; Williams et al. 2001). Thus, psychological, psychogenic and metabolic stressors act synergistically in compromising reproduction

526 (Marcus, Loucks, and Berga 2001; Giles and Berga 1993; Berga, Daniels, and Giles 1997; Warren et al.
527 1999; Williams, Berga, and Cameron 2007; Berga 2008). In line with these findings, severe mental or
528 infectious diseases such as HIV or Ebola infection have been found to add to the risk for FHA (Fava et al.
529 1984; Cejtin et al. 2018; Godwin et al. 2019). On this background, the current SARS-CoV-2 pandemic will
530 probably also influence the prevalence of FHA.
531
532 Substantial investigation has focused on examining the mechanisms through which immune, nutritional
533 and psychological stressors impact upon the reproductive axis (Li and O'Byrne 2015). Stress activates
534 multiple neural axes and results in elevated corticosteroid and prolactin concentrations. All of these
535 factors, in turn, can impact upon the functioning of the GnRH neuronal network (Li and O'Byrne 2015;
536 Mastorakos, Pavlatou, and Mizamtsidi 2006; Meczekalski et al. 2008; Williams, Berga, and Cameron 2007;
537 Berga and Girton 1989; Dobson et al. 2003). In many cases, it is difficult to tease apart the impacts of
538 nutritional and psychological stressors on fertility with a synergism between the two in operation (Berga
539 1997; Fioroni et al. 1994; Shanan et al. 1965; Chand and Lovejoy 2011; Mendelson 2013).
540
541 Cortisol: High cortisol levels are well known to be associated with amenorrhea (Berga, Daniels, and Giles
542 1997; Suh et al. 1988; Berga and Girton 1989; Brundu et al. 2006): Athletes with FHA as well as those with
543 eating disorders and amenorrhea have higher serum cortisol levels than women with a menstrual cycle
544 (Villanueva et al. 1986; Laughlin, Dominguez, and Yen 1998; Ackerman et al. 2012). Administration of
545 hydrocortisone reduces LH pulse frequency during the follicular phase of otherwise eumenorrheic women
546 (Saketos, Sharma, and Santoro 1993). Elevated circulating corticosteroids reduce LH pulse amplitude
547 (Petraglia et al. 1987; Olster and Ferin 1987; Breen et al. 2008; Dudas and Merchenthaler 2002; Saketos,
548 Sharma, and Santoro 1993) and suppress LH pulse frequency through an unknown central mechanism
549 (Ralph et al. 2016). Traumatic family events (sexual abuse, parental conflict, separation or death) have are
550 associated with elevated cortisol levels that can persist beyond the traumatic period (Flinn et al. 2011;
551 Jacobs, Boynton-Jarrett, and Harville 2015) and consequently present a long-term risk factor for FHA.

552 Cortisol seems to be one of the most important factors in return of menses. In women with a history of
553 eating disorders, and even after weight gain, serum levels of fasting cortisol tend to be lower in women
554 with return of menses compared to those without (Dei et al. 2008; Karountzos et al. 2017; Misra et al.
555 2006; Pitts et al. 2014; Tinahones et al. 2005; Arimura et al. 2010). Other studies confirmed significant
556 differences in cortisol levels between women with and without return of menses (Falsetti et al. 2002;
557 Jacoangeli et al. 2006; Miller et al. 1998) and two studies identified low serum cortisol levels as a predictor
558 for the return of menses (Arimura et al. 2010; Falsetti et al. 2002). Furthermore, women with a return of
559 menses after cognitive behavioral therapy had cortisol levels comparable to those of eumenorrheic
560 women (Berga, Daniels, and Giles 1997).
561
562 CRH: CRH suppresses pulsatile LH secretion but the pathway through which activated CRH neurons inhibit
563 GnRH secretion remains unclear (McCosh, Breen, and Kauffman 2019; Li and O'Byrne 2015). There is little
564 evidence for a direct modulation of GnRH neurons by CRH although effects of CRH on kisspeptin neurons
565 may exist (Raftogianni et al. 2018; McCosh, Breen, and Kauffman 2019).
566
567 Prolactin: Prolactin is released in response to stress in humans and animals (Levin, Jiang, and Kagan 2018;
568 Armario et al. 1996; Schedlowski et al. 1992; Theorell 1992; Sonino et al. 2004; Sobrinho 2003). Animal
569 studies show that prolactin acts through kisspeptin neurons to suppress pulsatile GnRH secretion and
570 infertility due to hyperprolactinemia can be reversed to some extent by treatment with kisspeptin (Sonigo
571 et al. 2012). Prolactin also raises secretion of ACTH and augments the adrenal cortex's sensitivity to ACTH,
572 thus resulting in high corticosterone release even with low levels of ACTH (Weber and Calogero 1991).
573
574 Adrenergic pathways
575 Acute stress results in the elevated secretion of catecholamines from the adrenal medulla and the
576 activation of brainstem adrenergic neurons (William Tank and Lee Wong 2014). The effects of adrenaline
577 and noradrenaline on LH secretion have been known for many decades (Sawyer 1975) but the precise

578 mechanisms through which they modulate GnRH secretion remain unclear (Herbison 2015). In general,
579 adrenergic inputs to the GnRH neuronal network are thought to exert a permissive role in enabling the
580 network to function optimally for both pulsatile and surge secretion (Herbison 1997; Anselmo-Franci et
581 al. 1997; Gallo et al. 1989, Scott and Clarke, 1993; Goodman et al., 1995). Nevertheless, in
582 gonadectomised animals, noradrenaline consistently suppresses pulsatile LH secretion (Herbison 1997).
583 Electrophysiological studies in mice have revealed that the activation of adrenergic receptors on GnRH
584 neurons was exclusively inhibitory (Han and Herbison 2008). Thus, it seems likely that the brainstem
585 adrenergic neurons innervate multiple components of the GnRH neuronal network where they may exert
586 different effects depending upon their level of activation (Herbison 1997). For example, under states of
587 heightened activation, they may provide a predominant direct inhibition of GnRH neurons to aid in the
588 suppression of pulsatile LH secretion.
589
590 The likelihood of occurrence of FHA and return of menses may be influenced by an individual's sensitivity
591 to stress. Evidence in humans and monkeys indicates that alterations in brain serotonin transmission play
592 a role in determining am individuals sensitivity to stress (Bethea, Centeno, and Cameron 2008; Tancer et
593 al., 1994; Ressler and Nemeroff, 2000; Bhagwagar et al., 2002). Stress-sensitive monkeys were found to
594 have diminished serotonergic activity and administration of a serotonin reuptake inhibitor (citalopram)
595 improves stress resilience (Lima et al. 2009; Bethea et al. 2005). Human and animal studies have also
596 indicated that a serotonin transporter gene variant is involved in individual stress susceptibility and
597 related suppression of LH secretion (Caspi et al. 2010; Caspi et al. 2003; Grabe et al. 2005; Michopoulos
598 et al. 2009). Notably, a decrease in ovarian steroid hormone concentrations was found to suppress
599 serotonin neural function in monkeys (Bethea et al. 2002; Bethea et al. 2005) but it remains unclear to
600 what extent circulating steroid levels are involved in maintaining FHA in women. Women with greater
601 stress resilience show a reduced risk for irregular menstrual cycles when experiencing low to moderate
602 chronic stress (Palm-Fischbacher and Ehlert 2014). However, no studies evaluating stress-resilience in the
603 context of resumption of menses have been conducted so far.

Lifestyle factors

Cigarette smoking is associated with higher rates of menstrual disorders (Buck et al. 1997; Howe et al. 1985). Several biologic mechanisms have been proposed to underlie this, such as actions on the hypothalamic-pituitary-ovarian axis, a direct toxic effect on the ovary, and alterations in peripheral estrogen production (Weisberg 1985). In a study of 2544 college students, cigarette smoking showed a dose-dependent relationship with the risk for FHA (Johnson and Whitaker 1992). Smoking more than one packet of cigarettes per day was associated with a 1.96 increased relative risk for persisting amenorrhea. Unfortunately, no information was available on the lifetime duration of smoking. The well-established association between smoking and lower BMI (Rasky, Stronegger, and Freidl 1996) is a potential confound but student smokers in that study had the same relative weight as non-smokers.

The effect of alcohol intake on the menstrual cycle has not been clearly established (Grodstein, Goldman, and Cramer 1994; Mello 1988). Recent moderate alcohol intake does not appear to have adverse short-term effects on menstrual cycle function (Schliep et al. 2015; Shilaih et al. 2017). The only study investigating alcohol intake in the context of prolonged amenorrhea showed no association between alcohol consumption and persistence of FHA (Johnson and Whitaker 1992). These findings have to be interpreted with caution as alcohol intake was self-reported.

Genetic factors

Genetic factors influence age at menarche (Dvornyk and Waqar ul 2012) and at menopause (Voorhuis et al. 2010) and will very likely also be involved in the regulation of the menstrual cycle. Rare gene variants associated with idiopathic hypogonadotropic hypogonadism in women with hypothalamic amenorrhea, may influence susceptibility to functional changes in GnRH secretion (Caronia et al. 2011). Also, in comparison to regularly menstruating runners, runners with FHA reported more eating disorders or major affective disorders in close kinship (Gadpaille, Sanborn, and Wagner 1987).

Treatment options trailed for re-onset and maintenance of menstruation

Medical treatment options for facilitating the recovery of menses include gonadal hormonal therapy (Falsetti et al. 2002; Genazzani et al. 2012; Shen, Xu, and Lin 2013), recombinant human leptin (metreleptin) (Chou et al. 2011; Welt et al. 2004) or opioid receptor blockers (naltrexone) (Genazzani et al. 1995). Altogether, six prospective studies are available (3 of low, 1 of middle and 2 of high quality).

Medication

Estrogen: The association between estrogens and female weight has been previously reported (Leeners et al. 2017). An increase in estradiol levels resulting from follicular maturation and conversion of androgens to estrogens in fat tissue (associated with weight gain) is confirmed in all of the studies investigating hormonal levels in resumption of menses (Arimura et al. 2010; Audi et al. 1998; Barakat et al. 2016; Cominato et al. 2014; Holtkamp et al. 2003; Jacoangeli et al. 2006; Karountzos et al. 2017; Pitts et al. 2014; Tokatly Latzer et al. 2019). Estrogen increases GnRH receptor gene expression and enhances the ability of FSH to induce expression of LH receptors and promote follicular growth (Turzillo, Nolan, and Nett 1998; Richards et al. 1976). This has generated the hypothesis that the pituitary response to GnRH and the ovarian response to gonadotropin could be reinforced with estrogen. However, studies evaluating this hypothesis failed to show any effect on the likelihood of recovery of menses (Falsetti et al. 2002; Genazzani et al. 2012; Shen, Xu, and Lin 2013).

Metreleptin: Recombinant human leptin (metreleptin) facilitated the recovery of menses in women with FHA due to low body weight, excessive exercise or unspecified reasons (Chou et al. 2011; Welt et al. 2004). With two daily subcutaneous doses (0.08-0.12 mg/kg body weight) to mimic normal diurnal patterns, recovery of menses occurred after 28 days up to 32 weeks (Welt et al. 2004; Chou et al. 2011; Wong et al. 2004). In women, without return of menses during the study period, continuous improvement of follicular maturation was confirmed by ultrasound and laboratory parameters (Welt et al. 2004). Important adverse effects of metreleptin application include a decrease in appetite that is counter-

656 productive to energy status (Welt et al. 2004; Chou et al. 2011). Although results are promising, further
657 investigations are necessary to determine the efficacy and safety of metreleptin treatment including dose-
658 finding and treatment duration studies in different background characteristics.
659
660 Naltrexone: The long-acting opioid receptor blocker naloxone increases LH pulse frequency and amplitude
661 in amenorrheic women (Quigley et al. 1980; Khoury et al. 1987) and, as such, naltrexone has been tested
662 to induce the recovery of menses. Administration of 50-150 mg/d was found to have no effect (Remorgida
663 et al. 1990), a moderate effect (Armeanu, Berkhout, and Schoemaker 1992), or full return of menses
664 (Wildt and Leyendecker 1987; Wildt et al. 1993). In the most recent placebo-controlled study, 24 (80%)
665 women with FHA due to weight loss reported menstrual bleeding within 90 days after initiation of
666 naltrexone therapy (Genazzani et al. 1995). After three months of treatment, LH plasma levels and pulse
667 amplitude increased whereas FSH plasma levels did not show any change. The recovery of menstrual
668 cycles occurred prior to weight gain, suggesting that naltrexone had a central effect independent from
669 body weight gain. Six months after naltrexone discontinuation, 75% of the women were still
670 eumenorrheic. Although only minor side effects such as nausea at the beginning of treatment have been
671 reported, further studies are necessary to determine the efficacy and safety in a larger sample of women
672 with FHA distinguished by its trigger.
673
674 *Psychotherapeutic interventions*
675 Women with FHA, especially those with eating disorders, often experience fear of weight gain, concerns
676 about dieting, weight judgements of others, perfectionistic performance standards, tendencies to engage
677 in binge eating, excessive exercise, or depressive symptoms (Fries, Nillius, and Pettersson 1974; Faust et
678 al. 2013; Brambilla et al. 2003; Favaro and Santonastaso 2009; Giles and Berga 1993; Marcus, Loucks, and
679 Berga 2001). Many of these characteristics can effectively be treated by CBT (Berga and Loucks 2006;
680 Berga et al. 2003; Michopoulos et al. 2013). CBT may successfully modify eating and exercise patterns,
681 maladaptive attitudes concerning body image and weight regulation as well as problem-solving

techniques (Marcus, Loucks, and Berga 2001; Giles and Berga 1993; Mountjoy et al. 2018; Pauli and Berga 2010). CBT has been shown to promote the return of menses alongside the recovery of cortisol or leptin levels (Berga, Daniels, and Giles 1997; Berga et al. 2003; Michopoulos et al. 2013; Berga and Loucks 2006). Besides CBT, hypnotherapy may be helpful in women with FHA (Tschugguel and Berga 2003). Coping skills such as relaxation, distress tolerance, meditation and mindfulness or yoga provided further positive effects (Katterman et al. 2014; Rani et al. 2011; Goyal et al. 2014; Hall et al. 2016; Berkman et al. 2006), but have not directly been investigated in their effect on recovery of menses.

Discussion

While disturbances of the menstrual cycle in association with weight loss and reduced energy balance are relatively well understood, knowledge on which conditions and whether menses recovers after FHA is rather limited. Recently published guidelines of the Endocrine Society provide well-founded recommendations for the diagnosis of FHA as well as the treatment of its consequences such as bone loss, infertility or eventual cardiovascular impairment (Gordon et al. 2017). The present review focusses on the **return of menses**, i.e. expand these guidelines into the physiology of recurrence of the menstrual cycle and options to end FHA.

Providing a comprehensive account of the return of menses after FHA is challenged by the many methodological differences used in study designs examining this issue and the difficulties in teasing out the impact of the influencing factors. Research groups use various definitions of FHA and also of the return of menses; for example, with regard to the total number of cycles requested, the regularity of cycles, or the presence of ovulation. Only 11 of the 31 studies exploring recovery of menses after FHA presented a definition of the return of menses and often the duration of initial amenorrhea is not reported. Most studies do not differentiate between full ovulatory cycles and partial recovery.

In addition, the conditions to be met to initiate the observation phase [i.e. body weight/BMI, energy

intake/expenditure, etc.] when return of menses can justifiably be expected, are often either not defined, not confirmed, or not controlled for stability during the observation phase. A further important point is the marked variation in the total length of the follow-up period.

We also note that many different approaches have been used to define and evaluate influencing factors such as measures of weight/body fat, energy balance, nutrition, psychological and lifestyle factors. Often, studies have not controlled for well-known hormonal causes of cycle disturbances and endocrine diseases. This is particularly important as, at present, we cannot distinguish between causes and consequences for most gut hormones, or other laboratory parameters. Differences in study groups related to causes of FHA, age, ethnicity, psychological background conditions and small sample sizes further challenge the generalizability of findings.

Only twelve studies had a prospective design and currently no prospective longitudinal studies exist with adequately powered study groups that control for relevant confounders to allow a reliable estimation of the frequency and timing of recovery of menses. Consequently, our knowledge of the prevalence of recovery of menses come from studies that are of a very limited quality. Today, we cannot identify women with an increased risk for long-term FHA even after weight/BMI and energy availability have been normalized. It is very likely that psychological factors and stress are involved in those women returning to normal weight without a return of menses (Gordon et al. 2017), but presently no studies on success rates of treatment concepts including both organic and psychological factors are available. Therefore, we can not as yet answer the question if the return of menses can be reliably achieved with adequate treatment.

While there is abundant research on the onset of the cycle during puberty and the initiation of amenorrhea in the case of weight loss or unfavourable energy balance, literature on the physiology of recovery of menses is virtually non-existent. Animal studies have allowed understanding of the regulation of the pulse generator and how different gut hormones interact with the GnRH neuronal network, but more research is needed, to better understand the regulatory mechanisms involved in the recovery of menses in women.

Although study designs vary considerably with regard to parameters and techniques chosen, research findings consistently support the importance of maintaining of a stable normal weight, a minimum amount of body fat and adequate energy availability for recovery of menses. However, we lack a reliable basis to suggest target weights or energy balance that would allow the recovery of menses in individual women. Also, we cannot predict if the menstrual cycle recovers after the normalization of weight and energy balance in individual women and how lifestyle or psychological factors are involved. Studies examining the association between sport and return of menses show higher chances of recovery in normal weight women when energy availability increases in most but not in all studies. The small number of study participants, self-reported food intake (known to be biased by underreporting) and limited precision of the evaluation of energy balance might explain differences in findings.

The calculation of nutritional needs based on total energy expenditure and sufficient carbohydrate and protein requirements derived from individual goals and sport-specific regimens is the major factor promoting the return of menses in athletes (Arends et al. 2012; Cialdella-Kam et al. 2014; Kopp-Woodroffe et al. 1999; Lagowska et al. 2014; Mallinson et al. 2013; Reed et al. 2015). In contrast, weight recovery is the most important factor in women with FHA due to eating disorders (Dempfle et al. 2013; Golden et al. 1997; Golden et al. 2008; Faust et al. 2013). While an indirect effect of psychological factors especially in the context of eating disorders is well established, the direct effect of previous and current psychological factors warrants further exploration. Very likely, subtle persisting characteristics of eating behaviours, exercise and energy balance are involved in augmenting the risk for prolonged amenorrhea but remain to be elucidated.

Overall, the time to return of menses seems to depend on the initial cause of FHA with shorter duration till recovery in athletes (Cialdella-Kam et al. 2014) compared to women with eating disorders (Karountzos et al. 2017). The inhomogeneity of studies and the lack of systemic consideration of influencing factors hampers development of good and robust prediction models.

Comparative studies or reviews on the effect of different treatment strategies to improve chances for return of menses do not exist. Interventions such as increase in weight/ energy availability or adaptation of nutrition have been confirmed to facilitate the return of menstruation, however, specific nutrition concepts have only been investigated in athletes. Stress management is part of the therapeutic approach with eating disorders, but its role to improve chances for return of menses has not been fully explored yet. In addition to the well-known strategies of adequate weight/BMI/percentage body fat, energy balance and psychological well-being, drugs as metreleptin or naltrexone have showed favourable results in some studies but need further investigation.

Open research questions

More methodologically well-designed studies are needed to close the present gap in our understanding on how the return of menses in FHA can be facilitated. This includes clear definitions and diagnostic criteria of FHA, return of menses, conditions at the beginning of an observation period, interventions and influencing factors/ potential confounders. Further research should address clinically relevant therapeutic targets values for weight, BMI and energy levels as well as overall chances for return of menses. Studies should be prospective, longitudinal and include control groups with medications and other therapeutic interventions tested in a placebo-controlled double-blind design, wherever possible. The pathophysiology of return of menses should also be evaluated in human studies, cover central and peripheral regulatory mechanisms, actual psychological stressors, early stress experiences, as well as genetic and epigenetic factors involved in biological and psychological influences. The latter could serve to identify women at risk for FHA and enable preventive measures.

Practical advice

Clinicians should inform women with FHA on the potential long-term consequences of amenorrhea and the likelihood for return of menses under adequate as well as inadequate conditions. Extensive counselling may be needed in the case of psychopathology or in high performance athletes. As FHA is

784 often the combined effect of low weight, excessive exercise, poor nutrition and psychological factors,
785 evaluation of the cause of amenorrhea should always include the exploration of all relevant factors and
786 be carefully differentiated from organic causes of amenorrhea. FHA can persist for several years even
787 after achieving healthy weight/ adequate energy balance and has severe long-term effects if not treated.
788 A such, it is important to aim as early as possible for normal cycle function. Therapeutic support should
789 include adequate nutrition, energy balance, exercise level and mental health. Ideally, support should be
790 provided by an interdisciplinary team of a gynaecologist-obstetrician, a dietitian and a mental health
791 professional. In particular, behavioural changes needed for the improvement of energy balance may
792 necessitate psychotherapeutic support. Non-drug treatment options that eliminate the causes of FHA
793 remain the therapy of choice to regain menstruation. Predicting if and when menses will return is difficult.
794 As the chances for pregnancy strongly rely on women's age (Leeners et al. 2013; Somigliana et al. 2016),
795 medically-assisted reproduction support should be discussed when menses do not reoccur despite
796 adequate nutrition, weight, energy balance and stress management.
797

798 Conclusion

799 Based on the limited evidence available, the restoration of adequate weight/BMI and energy balance have
800 a clear beneficial effect, but normalization of these factors alone does not reliably result in return of
801 menses. As the physiology of the return of menses and the underlying factors are only poorly understood,
802 it seems unlikely that a precise prediction model for when the menstrual cycle will recover in individual
803 women will be achieved in the near future. Given the severe impact of FHA on womens' overall and
804 reproductive health, there is a clear and urgent need for further research investigating the factors
805 allowing return of menses. Currently, a combination of adequate nutrition, weight, energy balance and
806 stress management still seems to be the most adequate approach to increase chances for the recovery of
807 menses after FHA.
808

Authors' roles

J.P and B.L. contributed to the identification and critical evaluation of the relevant literature, analysis of study results and to drafting the article including the critical discussion of findings. J.P. participated in preparation of the proposal, completed the initial literature research, drafted a first version of the article and participated in finalization of the article. A.H. provided his expertise on central regulatory mechanisms in return of menses, drafted and finalized related passages of the manuscript and critically revised the final version of the manuscript B.L. finalized the concept for the manuscript, supervised the literature research, data extraction and presentation of relevant data. She drafted and finalized different versions of the manuscript and critically revised the final version of the manuscript. All authors approved the final version of this manuscript.

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Conflicts of interest

None of the authors has any conflict of interest.

References

Abbate Daga G, Campisi S, Marzola E, Rocca G, Peris C, Campagnoli C, Peloso A, Vesco S, Rigardetto R, and Fassino S. Amenorrhea in eating disorders: poor stability of symptom after a one-year treatment. *Eat Weight Disord* 2012: **17**; e78-85.

Ackerman KE, Slusarz K, Guereca G, Pierce L, Slattery M, Mendes N, Herzog DB, and Misra M. Higher ghrelin and lower leptin secretion are associated with lower LH secretion in young amenorrheic athletes compared with eumenorrheic athletes and controls. *Am J Physiol Endocrinol Metab* 2012: **302**; E800-806.

Adams MR, Kaplan JR, and Koritnik DR. Psychosocial influences on ovarian endocrine and ovulatory function in Macaca fascicularis. *Physiol Behav* 1985: **35**; 935-940.

Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, and Flier JS. Role of leptin in the neuroendocrine response to fasting. *Nature* 1996: **382**; 250-252.

Allsworth JE, Clarke J, Peipert JF, Hebert MR, Cooper A, and Boardman LA. The influence of stress on the menstrual cycle among newly incarcerated women. *Women's health issues : official publication of the Jacobs Institute of Women's Health* 2007: **17**; 202-209.

American Society for Reproductive Medicine PC. Current evaluation of amenorrhea. *Fertil Steril* 2008: **90**; S219-225.
Andersen AE and Ryan GL. Eating disorders in the obstetric and gynecologic patient population. *Obstet Gynecol* 2009: **114**; 1353-1367.
Andrico S, Gambera A, Specchia C, Pellegrini C, Falsetti L, and Sartori E. Leptin in functional hypothalamic amenorrhoea. *Hum Reprod* 2002: **17**; 2043-2048.
Anselmo-Franci JA, Franci CR, Krulich L, Antunes-Rodrigues J, and McCann SM. Locus coeruleus lesions decrease norepinephrine input into the medial preoptic area and medial basal hypothalamus and block the LH, FSH and prolactin preovulatory surge. *Brain Res* 1997: **767**; 289-296.
Arends JC, Cheung MY, Barrack MT, and Nattiv A. Restoration of menses with nonpharmacologic therapy in college athletes with menstrual disturbances: a 5-year retrospective study. *Int J Sport Nutr Exerc Metab* 2012: **22**; 98-108.
Arimura C, Nozaki T, Takakura S, Kawai K, Takii M, Sudo N, and Kubo C. Predictors of menstrual resumption by patients with anorexia nervosa. *Eat Weight Disord* 2010: **15**; e226-233.
Armario A, Marti O, Molina T, de Pablo J, and Valdes M. Acute stress markers in humans: response of plasma glucose, cortisol and prolactin to two examinations differing in the anxiety they provoke. *Psychoneuroendocrinology* 1996: **21**; 17-24.
Armeanu MC, Berkhout GM, and Schoemaker J. Pulsatile luteinizing hormone secretion in hypothalamic amenorrhea, anorexia nervosa, and polycystic ovarian disease during naltrexone treatment. *Fertil Steril* 1992: **57**; 762-770.
Audi L, Mantzoros CS, Vidal-Puig A, Vargas D, Gussinye M, and Carrascosa A. Leptin in relation to resumption of menses in women with anorexia nervosa. *Mol Psychiatry* 1998: **3**; 544-547.
Barakat R, Oakley O, Kim H, Jin J, and Ko CJ. Extra-gonadal sites of estrogen biosynthesis and function. *BMB Rep* 2016: **49**; 488-496.
Barnhart KT and Schreiber CA. Return to fertility following discontinuation of oral contraceptives. *Fertil Steril* 2009: **91**; 659-663.
Beaglehole B, Mulder RT, Frampton CM, Boden JM, Newton-Howes G, and Bell CJ. Psychological distress and psychiatric disorder after natural disasters: systematic review and meta-analysis. *Br J Psychiatry* 2018: **213**; 716-722.
Benson JE, Engelbert-Fenton KA, and Eisenman PA. Nutritional aspects of amenorrhea in the female athlete triad. *Int J Sport Nutr* 1996: **6**; 134-145.
Berga S and Naftolin F. Neuroendocrine control of ovulation. *Gynecol Endocrinol* 2012: **28 Suppl 1**; 9-13.
Berga SL. Behaviorally induced reproductive compromise in women and men. *Semin Reprod Endocrinol* 1997: **15**; 47-53.
Berga SL. Stress and reprodution: a tale of false dichotomy? *Endocrinology* 2008: **149**; 867-868.
Berga SL, Daniels TL, and Giles DE. Women with functional hypothalamic amenorrhea but not other forms of anovulation display amplified cortisol concentrations. *Fertil Steril* 1997: **67**; 1024-1030.
Berga SL and Girton LG. The psychoneuroendocrinology of functional hypothalamic amenorrhea. *Psychiatr Clin North Am* 1989: **12**; 105-116.
Berga SL and Loucks TL. Use of cognitive behavior therapy for functional hypothalamic amenorrhea. *Ann N Y Acad Sci* 2006: **1092**; 114-129.

888 Berga SL, Marcus MD, Loucks TL, Hlastala S, Ringham R, and Krohn MA. Recovery of ovarian
889 activity in women with functional hypothalamic amenorrhea who were treated with
890 cognitive behavior therapy. *Fertil Steril* 2003: **80**; 976-981.
891 Berkman ND, Bulik CM, Brownley KA, Lohr KN, Sedway JA, Rooks A, and Gartlehner G.
892 Management of eating disorders. *Evid Rep Technol Assess (Full Rep)* 2006; 1-166.
893 Berner LA, Feig EH, Witt AA, and Lowe MR. Menstrual cycle loss and resumption among
894 patients with anorexia nervosa spectrum eating disorders: Is relative or absolute weight
895 more influential? *Int J Eat Disord* 2017: **50**; 442-446.
896 Bethea CL, Centeno ML, and Cameron JL. Neurobiology of stress-induced reproductive
897 dysfunction in female macaques. *Molecular neurobiology* 2008: **38**; 199-230.
898 Bethea CL, Lu NZ, Gundlah C, and Streicher JM. Diverse actions of ovarian steroids in the
899 serotonin neural system. *Front Neuroendocrinol* 2002: **23**; 41-100.
900 Bethea CL, Pau FKY, Fox S, Hess DL, Berga SL, and Cameron JL. Sensitivity to stress-induced
901 reproductive dysfunction linked to activity of the serotonin system. *Fertility and Sterility*
902 2005: **83**; 148-155.
903 Bodell LP and Mayer LES. Percent body fat is a risk factor for relapse in anorexia nervosa: a
904 replication study. *Int J Eat Disord* 2011: **44**; 118-123.
905 Bomba M, Gambera A, Bonini L, Peroni M, Neri F, Scagliola P, and Nacinovich R. Endocrine
906 profiles and neuropsychologic correlates of functional hypothalamic amenorrhea in
907 adolescents. *Fertil Steril* 2007: **87**; 876-885.
908 Brambilla F, Monteleone P, Bortolotti F, Dalle Grave R, Todisco P, Favaro A, Santonastaso P,
909 Ramacciotti C, Paoli R, and Maj M. Persistent amenorrhoea in weight-recovered
910 anorexics: psychological and biological aspects. *Psychiatry Research* 2003: **118**; 249-257.
911 Breen KM, Davis TL, Doro LC, Nett TM, Oakley AE, Padmanabhan V, Rispoli LA, Wagenmaker ER,
912 and Karsch FJ. Insight into the neuroendocrine site and cellular mechanism by which
913 cortisol suppresses pituitary responsiveness to gonadotropin-releasing hormone.
914 *Endocrinology* 2008: **149**; 767-773.
915 Brothers KJ, Wu S, DiVall SA, Messmer MR, Kahn CR, Miller RS, Radovick S, Wondisford FE, and
916 Wolfe A. Rescue of obesity-induced infertility in female mice due to a pituitary-specific
917 knockout of the insulin receptor. *Cell Metab* 2010: **12**; 295-305.
918 Brown E, Bain J, Lerner P, and Shaul D. Psychological, hormonal, and weight disturbances in
919 functional amenorrhea. *Can J Psychiatry* 1983: **28**; 624-628.
920 Brundu B, Loucks TL, Adler LJ, Cameron JL, and Berga SL. Increased cortisol in the cerebrospinal
921 fluid of women with functional hypothalamic amenorrhea. *J Clin Endocrinol Metab*
922 2006: **91**; 1561-1565.
923 Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Muller-
924 Wieland D, and Kahn CR. Role of brain insulin receptor in control of body weight and
925 reproduction. *Science* 2000: **289**; 2122-2125.
926 Buck GM, Sever LE, Batt RE, and Mendola P. Life-style factors and female infertility.
927 *Epidemiology* 1997: **8**; 435-441.
928 Bullen BA, Skrinar GS, Beitins IZ, von Mering G, Turnbull BA, and McArthur JW. Induction of
929 menstrual disorders by strenuous exercise in untrained women. *N Engl J Med* 1985: **312**;
930 1349-1353.
931 Cameron JL. Regulation of reproductive hormone secretion in primates by short-term changes
932 in nutrition. *Rev Reprod* 1996: **1**; 117-126.

933 Caronia LM, Martin C, Welt CK, Sykiotis GP, Quinton R, Thambundit A, Avbelj M, Dhruvakumar
934 S, Plummer L, Hughes VA*, et al.* A genetic basis for functional hypothalamic amenorrhea.
935 *N Engl J Med* 2011: **364**; 215-225.
936 Caspi A, Hariri AR, Holmes A, Uher R, and Moffitt TE. Genetic sensitivity to the environment: the
937 case of the serotonin transporter gene and its implications for studying complex
938 diseases and traits. *Am J Psychiatry* 2010: **167**; 509-527.
939 Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J,
940 Braithwaite A*, et al.* Influence of life stress on depression: moderation by a
941 polymorphism in the 5-HTT gene. *Science* 2003: **301**; 386-389.
942 Castellano JM and Tena-Sempere M. Metabolic control of female puberty: potential
943 therapeutic targets. *Expert Opin Ther Targets* 2016: **20**; 1181-1193.
944 Cejtin HE, Evans CT, Greenblatt R, Minkoff H, Weber KM, Wright R, Colie C, Golub E, and
945 Massad LS. Prolonged Amenorrhea and Resumption of Menses in Women with HIV. *J*
946 *Womens Health (Larchmt)* 2018.
947 Chand D and Lovejoy DA. Stress and reproduction: controversies and challenges. *Gen Comp*
948 *Endocrinol* 2011: **171**; 253-257.
949 Chianese R, Colledge WH, Fasano S, and Meccariello R. Editorial: The Multiple Facets of
950 Kisspeptin Activity in Biological Systems. *Front Endocrinol (Lausanne)* 2018: **9**; 727.
951 Chou SH, Chamberland JP, Liu X, Matarese G, Gao C, Stefanakis R, Brinkoetter MT, Gong H,
952 Arampatzi K, and Mantzoros CS. Leptin is an effective treatment for hypothalamic
953 amenorrhea. *Proc Natl Acad Sci U S A* 2011: **108**; 6585-6590.
954 Christo K, Cord J, Mendes N, Miller KK, Goldstein MA, Klibanski A, and Misra M. Acylated ghrelin
955 and leptin in adolescent athletes with amenorrhea, eumenorrheic athletes and controls:
956 a cross-sectional study. *Clin Endocrinol (Oxf)* 2008: **69**; 628-633.
957 Cialdella-Kam L, Guebels CP, Maddalozzo GF, and Manore MM. Dietary intervention restored
958 menses in female athletes with exercise-associated menstrual dysfunction with limited
959 impact on bone and muscle health. *Nutrients* 2014: **6**; 3018-3039.
960 Collaborative Group HFiBC. Type and timing of menopausal hormone therapy and breast cancer
961 risk: individual participant meta-analysis of the worldwide epidemiological evidence.
962 *Lancet* 2019: **394**; 1159-1168.
963 Cominato L, da Silva MM, Steinmetz L, Pinzon V, Fleitlich-Bilyk B, and Damiani D. Menstrual
964 cycle recovery in patients with anorexia nervosa: the importance of insulin-like growth
965 factor 1. *Horm Res Paediatr* 2014: **82**; 319-323.
966 Craig J, Zhu H, Dyce PW, Petrik J, and Li J. Leptin enhances oocyte nuclear and cytoplasmic
967 maturation via the mitogen-activated protein kinase pathway. *Endocrinology* 2004: **145**;
968 5355-5363.
969 Dan-Goor M, Sasson S, Davarashvili A, and Almagor M. Expression of glucose transporter and
970 glucose uptake in human oocytes and preimplantation embryos. *Hum Reprod* 1997: **12**;
971 2508-2510.
972 Davis AR, Kroll R, Soltes B, Zhang N, Grubb GS, and Constantine GD. Occurrence of menses or
973 pregnancy after cessation of a continuous oral contraceptive. *Fertil Steril* 2008: **89**;
974 1059-1063.
975 Davis C and Claridge G. The eating disorders as addiction: a psychobiological perspective. *Addict*
976 *Behav* 1998: **23**; 463-475.
977 De Souza MJ, Leidy HJ, O'Donnell E, Lasley B, and Williams NI. Fasting ghrelin levels in physically
978 active women: relationship with menstrual disturbances and metabolic hormones. *J Clin*
979 *Endocrinol Metab* 2004: **89**; 3536-3542.

Dei M, Seravalli V, Bruni V, Balzi D, and Pasqua A. Predictors of recovery of ovarian function after weight gain in subjects with amenorrhea related to restrictive eating disorders. *Gynecol Endocrinol* 2008: **24**; 459-464.

Dempfle A, Herpertz-Dahlmann B, Timmesfeld N, Schwarte R, Egberts KM, Pfeiffer E, Fleischhaker C, Wewetzer C, and Buhren K. Predictors of the resumption of menses in adolescent anorexia nervosa. *BMC Psychiatry* 2013: **13**; 308.

Divall SA, Williams TR, Carver SE, Koch L, Bruning JC, Kahn CR, Wondisford F, Radovick S, and Wolfe A. Divergent roles of growth factors in the GnRH regulation of puberty in mice. *J Clin Invest* 2010: **120**; 2900-2909.

Dobson H, Ghuman S, Prabhakar S, and Smith R. A conceptual model of the influence of stress on female reproduction. *Reproduction* 2003: **125**; 151-163.

Dominko T and First NL. Timing of meiotic progression in bovine oocytes and its effect on early embryo development. *Mol Reprod Dev* 1997: **47**; 456-467.

Donato J, Jr., Cravo RM, Frazao R, Gautron L, Scott MM, Lachey J, Castro IA, Margatho LO, Lee S, Lee C*, et al.* Leptin's effect on puberty in mice is relayed by the ventral premammillary nucleus and does not require signaling in Kiss1 neurons. *J Clin Invest* 2011: **121**; 355-368.

Drew FL. The epidemiology of secondary amenorrhea. *J Chronic Dis* 1961: **14**; 396-407.

Dudas B and Merchenthaler I. Close juxtapositions between luteinizing hormone-releasing hormone-immunoreactive neurons and corticotropin-releasing factor-immunoreactive axons in the human diencephalon. *J Clin Endocrinol Metab* 2002: **87**; 5778-5784.

Dueck CA, Matt KS, Manore MM, and Skinner JS. Treatment of athletic amenorrhea with a diet and training intervention program. *Int J Sport Nutr* 1996: **6**; 24-40.

Dvornyk V and Waqar ul H. Genetics of age at menarche: a systematic review. *Hum Reprod Update* 2012: **18**; 198-210.

El Ghoch M, Alberti M, Milanese C, Battistini NC, Pellegrini M, Capelli C, Calugi S, and Dalle Grave R. Comparison between dual-energy X-ray absorptiometry and skinfolds thickness in assessing body fat in anorexia nervosa before and after weight restoration. *Clin Nutr* 2012: **31**; 911-916.

El Ghoch M, Calugi S, Chignola E, Bazzani PV, and Dalle Grave R. Body fat and menstrual resumption in adult females with anorexia nervosa: a 1-year longitudinal study. *J Hum Nutr Diet* 2016: **29**; 662-666.

Elliott-Sale KJ, Tenforde AS, Parziale AL, Holtzman B, and Ackerman KE. Endocrine Effects of Relative Energy Deficiency in Sport. *Int J Sport Nutr Exerc Metab* 2018: **28**; 335-349.

Evans MC and Anderson GM. Neuroendocrine integration of nutritional signals on reproduction. *J Mol Endocrinol* 2017: **58**; R107-r128.

Facchinetti F, Fava M, Fioroni L, Genazzani AD, and Genazzani AR. Stressful life events and affective disorders inhibit pulsatile LH secretion in hypothalamic amenorrhea. *Psychoneuroendocrinology* 1993: **18**; 397-404.

Falsetti L, Gambera A, Barbetti L, and Specchia C. Long-term follow-up of functional hypothalamic amenorrhea and prognostic factors. *J Clin Endocrinol Metab* 2002: **87**; 500-505.

Faust JP, Goldschmidt AB, Anderson KE, Glunz C, Brown M, Loeb KL, Katzman DK, and Le Grange D. Resumption of menses in anorexia nervosa during a course of family-based treatment. *J Eat Disord* 2013: **1**; 12.

Fava GA, Trombini G, Grandi S, Bernardi M, Evangelisti LP, Santarsiero G, and Orlandi C. Depression and anxiety associated with secondary amenorrhea. *Psychosomatics* 1984: **25**; 905-908.

Favaro A and Santonastaso P. Seasonality and the prediction of weight at resumption of menses in anorexia nervosa. *Fertil Steril* 2009: **91**; 1395-1397.

Fernandez-Fernandez R, Martini AC, Navarro VM, Castellano JM, Dieguez C, Aguilar E, Pinilla L, and Tena-Sempere M. Novel signals for the integration of energy balance and reproduction. *Mol Cell Endocrinol* 2006: **254-255**; 127-132.

Filova B, Malinova M, Babickova J, Tothova L, Ostatnikova D, Celec P, and Hodosy J. Effects of testosterone and estradiol on anxiety and depressive-like behavior via a non-genomic pathway. *Neurosci Bull* 2015: **31**; 288-296.

Fioroni L, Fava M, Genazzani AD, Facchinetti F, and Genazzani AR. Life events impact in patients with secondary amenorrhoea. *J Psychosom Res* 1994: **38**; 617-622.

Flier JS. Clinical review 94: What's in a name? In search of leptin's physiologic role. *J Clin Endocrinol Metab* 1998: **83**; 1407-1413.

Flinn MV, Nepomnaschy PA, Muehlenbein MP, and Ponzi D. Evolutionary functions of early social modulation of hypothalamic-pituitary-adrenal axis development in humans. *Neurosci Biobehav Rev* 2011: **35**; 1611-1629.

Freimuth M, Moniz S, and Kim SR. Clarifying exercise addiction: differential diagnosis, co-occurring disorders, and phases of addiction. *Int J Environ Res Public Health* 2011: **8**; 4069-4081.

Fries H, Nillius SJ, and Pettersson F. Epidemiology of secondary amenorrhea. II. A retrospective evaluation of etiology with special regard to psychogenic factors and weight loss. *Am J Obstet Gynecol* 1974: **118**; 473-479.

Frisancho AR. New standards of weight and body composition by frame size and height for assessment of nutritional status of adults and the elderly. *Am J Clin Nutr* 1984: **40**; 808-819.

Frisch RE. Body fat, menarche, fitness and fertility. *Hum Reprod* 1987: **2**; 521-533.

Frisch RE and McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. *Science* 1974: **185**; 949-951.

Gadpaille WJ, Sanborn CF, and Wagner WW, Jr. Athletic amenorrhea, major affective disorders, and eating disorders. *Am J Psychiatry* 1987: **144**; 939-942.

Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, and Riley D. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. *Glob Adv Health Med* 2013: **2**; 38-43.

Garcia-Garcia RM. Integrative control of energy balance and reproduction in females. *ISRN Vet Sci* 2012: **2012**; 121389.

Gaytan F, Barreiro ML, Chopin LK, Herington AC, Morales C, Pinilla L, Casanueva FF, Aguilar E, Dieguez C, and Tena-Sempere M. Immunolocalization of ghrelin and its functional receptor, the type 1a growth hormone secretagogue receptor, in the cyclic human ovary. *J Clin Endocrinol Metab* 2003: **88**; 879-887.

Gaytan F, Morales C, Barreiro ML, Jeffery P, Chopin LK, Herington AC, Casanueva FF, Aguilar E, Dieguez C, and Tena-Sempere M. Expression of growth hormone secretagogue receptor type 1a, the functional ghrelin receptor, in human ovarian surface epithelium, mullerian duct derivatives, and ovarian tumors. *J Clin Endocrinol Metab* 2005: **90**; 1798-1804.

Genazzani AD, Chierchia E, Santagni S, Rattighieri E, Farinetti A, and Lanzoni C. Hypothalamic amenorrhea: from diagnosis to therapeutical approach. *Ann Endocrinol (Paris)* 2010: **71**; 163-169.

Genazzani AD, Meczekalski B, Podfigurna-Stopa A, Santagni S, Rattighieri E, Ricchieri F, Chierchia E, and Simoncini T. Estriol administration modulates luteinizing hormone secretion in women with functional hypothalamic amenorrhea. *Fertil Steril* 2012: **97**; 483-488.

Genazzani AD, Petraglia F, Gastaldi M, Volpogni C, Gamba O, and Genazzani AR. Naltrexone treatment restores menstrual cycles in patients with weight loss-related amenorrhea. *Fertil Steril* 1995: **64**; 951-956.

Genazzani AD, Petraglia F, Gastaldi M, Volpogni C, Gamba O, and Genazzani AR. Naltrexone treatment restores menstrual cycles in patients with weight loss-related amenorrhea*. *Fertility and Sterility* 1995: **64**; 951-956.

Giles DE and Berga SL. Cognitive and psychiatric correlates of functional hypothalamic amenorrhea: a controlled comparison. *Fertil Steril* 1993: **60**; 486-492.

Godwin CL, Wohl DA, Fischer Nd WA, Singh K, Hawks DA, Devore EE, and Brown J. Reproductive health sequelae among women who survived Ebola virus disease in Liberia. *Int J Gynaecol Obstet* 2019: **146**; 212-217.

Golden NH, Jacobson MS, Schebendach J, Solanto MV, Hertz SM, and Shenker IR. Resumption of menses in anorexia nervosa. *Arch Pediatr Adolesc Med* 1997: **151**; 16-21.

Golden NH, Jacobson MS, Sterling WM, and Hertz S. Treatment goal weight in adolescents with anorexia nervosa: use of BMI percentiles. *Int J Eat Disord* 2008: **41**; 301-306.

Gordley LB, Lemasters G, Simpson SR, and Yiin JH. Menstrual disorders and occupational, stress, and racial factors among military personnel. *J Occup Environ Med* 2000: **42**; 871-881.

Gordon CM. Clinical practice. Functional hypothalamic amenorrhea. *N Engl J Med* 2010: **363**; 365-371.

Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, Murad MH, Santoro NF, and Warren MP. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2017: **102**; 1413-1439.

Goyal M, Singh S, Sibinga EMS, Gould NF, Rowland-Seymour A, Sharma R, Berger Z, Sleicher D, Maron DD, Shihab HM*, et al.* Meditation Programs for Psychological Stress and Well-being: A Systematic Review and Meta-analysis. *JAMA Internal Medicine* 2014: **174**; 357-368.

Grabe HJ, Lange M, Wolff B, Volzke H, Lucht M, Freyberger HJ, John U, and Cascorbi I. Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. *Mol Psychiatry* 2005: **10**; 220-224.

Grinspoon SK, Askari H, Landt ML, Nathan DM, Schoenfeld DA, Hayden DL, Laposata M, Hubbard J, and Klibanski A. Effects of fasting and glucose infusion on basal and overnight leptin concentrations in normal-weight women. *Am J Clin Nutr* 1997: **66**; 1352-1356.

Grodstein F, Goldman MB, and Cramer DW. Infertility in women and moderate alcohol use. *Am J Public Health* 1994: **84**; 1429-1432.

Hall A, Ofei-Tenkorang NA, Machan JT, and Gordon CM. Use of yoga in outpatient eating disorder treatment: a pilot study. *J Eat Disord* 2016: **4**; 38.

Han S-K and Herbison AE. Norepinephrine Suppresses Gonadotropin-Releasing Hormone Neuron Excitability in the Adult Mouse. *Endocrinology* 2008: **149**; 1129-1135.

1117 Harlow SD and Matanoski GM. The association between weight, physical activity, and stress
1118 and variation in the length of the menstrual cycle. *Am J Epidemiol* 1991: **133**; 38-49.
1119 Herbison AE. Noradrenergic regulation of cyclic GnRH secretion. *Rev Reprod* 1997: **2**; 1-6.
1120 Herbison AE. Control of puberty onset and fertility by gonadotropin-releasing hormone
1121 neurons. *Nat Rev Endocrinol* 2016: **12**; 452-466.
1122 Herbison AE. The Gonadotropin-Releasing Hormone Pulse Generator. *Endocrinology* 2018: **159**;
1123 3723-3736.
1124 Hessler S, Liu X, and Herbison AE. Direct inhibition of arcuate kisspeptin neurones by
1125 neuropeptide Y in the male and female mouse. *J Neuroendocrinol* 2020: **32**; e12849.
1126 Hilton LK and Loucks AB. Low energy availability, not exercise stress, suppresses the diurnal
1127 rhythm of leptin in healthy young women. *Am J Physiol Endocrinol Metab* 2000: **278**;
1128 E43-49.
1129 Holtkamp K, Mika C, Grzella I, Heer M, Pak H, Hebebrand J, and Herpertz-Dahlmann B.
1130 Reproductive function during weight gain in anorexia nervosa. Leptin represents a
1131 metabolic gate to gonadotropin secretion. *J Neural Transm (Vienna)* 2003: **110**; 427-435.
1132 Holtzman B and Ackerman KE. Measurement, Determinants, and Implications of Energy Intake
1133 in Athletes. *Nutrients* 2019: **11**.
1134 Howe G, Westhoff C, Vessey M, and Yeates D. Effects of age, cigarette smoking, and other
1135 factors on fertility: findings in a large prospective study. *Br Med J (Clin Res Ed)* 1985:
1136 **290**; 1697-1700.
1137 Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, and Eghbali M. The protective role
1138 of estrogen and estrogen receptors in cardiovascular disease and the controversial use
1139 of estrogen therapy. *Biol Sex Differ* 2017: **8**; 33.
1140 Jacoangeli F, Masala S, Staar Mezzasalma F, Fiori R, Martinetti A, Ficoneri C, Novi B, Pierangeli S,
1141 Marchetti G, Simonetti G*, et al.* Amenorrhea after weight recover in anorexia nervosa:
1142 role of body composition and endocrine abnormalities. *Eat Weight Disord* 2006: **11**;
1143 e20-26.
1144 Jacobs HS, Knuth UA, Hull MG, and Franks S. Post-"pill" amenorrhoea--cause or coincidence? *Br*
1145 *Med J* 1977: **2**; 940-942.
1146 Jacobs MB, Boynton-Jarrett RD, and Harville EW. Adverse childhood event experiences, fertility
1147 difficulties and menstrual cycle characteristics. *J Psychosom Obstet Gynaecol* 2015: **36**;
1148 46-57.
1149 Jimerson DC, Mantzoros C, Wolfe BE, and Metzger ED. Decreased serum leptin in bulimia
1150 nervosa. *J Clin Endocrinol Metab* 2000: **85**; 4511-4514.
1151 Joffe H, Kim DR, Foris JM, Baldassano CF, Gyulai L, Hwang CH, McLaughlin WL, Sachs GS, Thase
1152 ME, Harlow BL*, et al.* Menstrual dysfunction prior to onset of psychiatric illness is
1153 reported more commonly by women with bipolar disorder than by women with
1154 unipolar depression and healthy controls. *J Clin Psychiatry* 2006: **67**; 297-304.
1155 Johnson J and Whitaker AH. Adolescent smoking, weight changes, and binge-purge behavior:
1156 associations with secondary amenorrhea. *Am J Public Health* 1992: **82**; 47-54.
1157 Karountzos V, Lambrinoudaki I, Tsitsika A, and Deligeoroglou E. The role of total body fat mass
1158 and trunk fat mass, combined with other endocrine factors, in menstrual recovery and
1159 psychopathology of adolescents with Anorexia Nervosa. *Gynecol Endocrinol* 2017: **33**;
1160 757-762.
1161 Katterman SN, Kleinman BM, Hood MM, Nackers LM, and Corsica JA. Mindfulness meditation
1162 as an intervention for binge eating, emotional eating, and weight loss: a systematic
1163 review. *Eat Behav* 2014: **15**; 197-204.

Katz P, Showstack J, Smith JF, Nachtigall RD, Millstein SG, Wing H, Eisenberg ML, Pasch LA, Croughan MS, and Adler N. Costs of infertility treatment: results from an 18-month prospective cohort study. *Fertil Steril* 2011: **95**; 915-921.

Keski-Rahkonen A and Mustelin L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. *Curr Opin Psychiatry* 2016: **29**; 340-345.

Khoury SA, Reame NE, Kelch RP, and Marshall JC. Diurnal patterns of pulsatile luteinizing hormone secretion in hypothalamic amenorrhea: reproducibility and responses to opiate blockade and an alpha 2-adrenergic agonist. *J Clin Endocrinol Metab* 1987: **64**; 755-762.

Kluge M, Schussler P, Schmidt D, Uhr M, and Steiger A. Ghrelin suppresses secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in women. *J Clin Endocrinol Metab* 2012: **97**; E448-451.

Kohmura H, Miyake A, Aono T, and Tanizawa O. Recovery of reproductive function in patients with anorexia nervosa: a 10-year follow-up study. *Eur J Obstet Gynecol Reprod Biol* 1986: **22**; 293-296.

Kondoh Y, Uemura T, Murase M, Yokoi N, Ishikawa M, and Hirahara F. A longitudinal study of disturbances of the hypothalamic-pituitary-adrenal axis in women with progestin-negative functional hypothalamic amenorrhea. *Fertil Steril* 2001: **76**; 748-752.

Kopp-Woodroffe SA, Manore MM, Dueck CA, Skinner JS, and Matt KS. Energy and nutrient status of amenorrheic athletes participating in a diet and exercise training intervention program. *Int J Sport Nutr* 1999: **9**; 70-88.

Kopp W, Blum WF, von Prittwitz S, Ziegler A, Lubbert H, Emons G, Herzog W, Herpertz S, Deter HC, Remschmidt H*, et al.* Low leptin levels predict amenorrhea in underweight and eating disordered females. *Mol Psychiatry* 1997: **2**; 335-340.

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, and Johnson CL. CDC growth charts: United States. *Adv Data* 2000; 1-27.

Lado-Abeal J, Clapper JA, Chen Zhu B, Hough CM, Syapin PJ, and Norman RL. Hypoglycemia-induced suppression of luteinizing hormone (LH) secretion in intact female rhesus macaques: role of vasopressin and endogenous opioids. *Stress* 2002: **5**; 113-119.

Lagowska K, Kapczuk K, Friebe Z, and Bajerska J. Effects of dietary intervention in young female athletes with menstrual disorders. *J Int Soc Sports Nutr* 2014: **11**; 21.

Lateef OM and Akintubosun MO. Sleep and Reproductive Health. *Journal of circadian rhythms* 2020: **18**; 1-1.

Laughlin GA, Dominguez CE, and Yen SS. Nutritional and endocrine-metabolic aberrations in women with functional hypothalamic amenorrhea. *J Clin Endocrinol Metab* 1998: **83**; 25-32.

Laughlin GA and Yen SS. Nutritional and endocrine-metabolic aberrations in amenorrheic athletes. *J Clin Endocrinol Metab* 1996: **81**; 4301-4309.

Lawson EA, Donoho D, Miller KK, Misra M, Meenaghan E, Lydecker J, Wexler T, Herzog DB, and Klibanski A. Hypercortisolemia is associated with severity of bone loss and depression in hypothalamic amenorrhea and anorexia nervosa. *J Clin Endocrinol Metab* 2009: **94**; 4710-4716.

Le Grange D, Doyle PM, Swanson SA, Ludwig K, Glunz C, and Kreipe RE. Calculation of expected body weight in adolescents with eating disorders. *Pediatrics* 2012: **129**; e438-446.

Leeners B, Geary N, Tobler PN, and Asarian L. Ovarian hormones and obesity. *Hum Reprod Update* 2017: **23**; 300-321.

1211 Leeners B, Geraedts K, Imthurn B, and Stiller R. The relevance of age in female human
1212 reproduction--current situation in Switzerland and pathophysiological background from
1213 a comparative perspective. *Gen Comp Endocrinol* 2013: **188**; 166-174.
1214 Leeners B, Stiller R, Block E, Gorres G, Imthurn B, and Rath W. Effect of childhood sexual abuse
1215 on gynecologic care as an adult. *Psychosomatics* 2007: **48**; 385-393.
1216 Levin VA, Jiang X, and Kagan R. Estrogen therapy for osteoporosis in the modern era.
1217 *Osteoporos Int* 2018: **29**; 1049-1055.
1218 Li XF and O'Byrne. Stress and the reproductive system. *Knobil and Neill's Physiology of*
1219 *Reproduction* 2015: **2**; 1637-1660.
1220 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ,
1221 Kleijnen J, and Moher D. The PRISMA statement for reporting systematic reviews and
1222 meta-analyses of studies that evaluate health care interventions: explanation and
1223 elaboration. *J Clin Epidemiol* 2009: **62**; e1-34.
1224 Lieberman JL, MJ DES, Wagstaff DA, and Williams NI. Menstrual Disruption with Exercise Is Not
1225 Linked to an Energy Availability Threshold. *Med Sci Sports Exerc* 2018: **50**; 551-561.
1226 Lima FB, Centeno ML, Costa ME, Reddy AP, Cameron JL, and Bethea CL. Stress sensitive female
1227 macaques have decreased fifth Ewing variant (Fev) and serotonin-related gene
1228 expression that is not reversed by citalopram. *Neuroscience* 2009: **164**; 676-691.
1229 Loucks AB, Kiens B, and Wright HH. Energy availability in athletes. *J Sports Sci* 2011: **29 Suppl 1**;
1230 S7-15.
1231 Loucks AB, Mortola JF, Girton L, and Yen SS. Alterations in the hypothalamic-pituitary-ovarian
1232 and the hypothalamic-pituitary-adrenal axes in athletic women. *J Clin Endocrinol Metab*
1233 1989: **68**; 402-411.
1234 Loucks AB and Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy
1235 availability in regularly menstruating women. *J Clin Endocrinol Metab* 2003: **88**; 297-311.
1236 Loucks AB, Verdun M, and Heath EM. Low energy availability, not stress of exercise, alters LH
1237 pulsatility in exercising women. *J Appl Physiol (1985)* 1998: **84**; 37-46.
1238 Magliano DJ, Rogers SL, Abramson MJ, and Tonkin AM. Hormone therapy and cardiovascular
1239 disease: a systematic review and meta-analysis. *Bjog* 2006: **113**; 5-14.
1240 Mallinson RJ, Williams NI, Olmsted MP, Scheid JL, Riddle ES, and De Souza MJ. A case report of
1241 recovery of menstrual function following a nutritional intervention in two exercising
1242 women with amenorrhea of varying duration. *J Int Soc Sports Nutr* 2013: **10**; 34.
1243 Manonai J, Chittacharoen A, and Theppisai U. Effect of estradiol valerate and levonorgestrel on
1244 vaginal health. *Eur J Obstet Gynecol Reprod Biol* 2004: **115**; 190-193.
1245 Manore MM, Kam LC, and Loucks AB. The female athlete triad: components, nutrition issues,
1246 and health consequences. *J Sports Sci* 2007: **25 Suppl 1**; S61-71.
1247 Mantzoros C, Flier JS, Lesem MD, Brewerton TD, and Jimerson DC. Cerebrospinal fluid leptin in
1248 anorexia nervosa: correlation with nutritional status and potential role in resistance to
1249 weight gain. *J Clin Endocrinol Metab* 1997: **82**; 1845-1851.
1250 Marcus MD, Loucks TL, and Berga SL. Psychological correlates of functional hypothalamic
1251 amenorrhea. *Fertil Steril* 2001: **76**; 310-316.
1252 Marjoribanks J, Farquhar C, Roberts H, Lethaby A, and Lee J. Long-term hormone therapy for
1253 perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 2017: **1**;
1254 Cd004143.
1255 Martini MG, Solmi F, Krug I, Karwautz A, Wagner G, Fernandez-Aranda F, Treasure J, and Micali
1256 N. Associations between eating disorder diagnoses, behaviors, and menstrual
1257 dysfunction in a clinical sample. *Arch Womens Ment Health* 2016: **19**; 553-557.

1258 Mastorakos G, Pavlatou MG, and Mizamtsidi M. The hypothalamic-pituitary-adrenal and the
1259 hypothalamic- pituitary-gonadal axes interplay. *Pediatr Endocrinol Rev* 2006: **3 Suppl 1**;
1260 172-181.
1261 Mayer LE, Klein DA, Black E, Attia E, Shen W, Mao X, Shungu DC, Punyanita M, Gallagher D,
1262 Wang J*, et al.* Adipose tissue distribution after weight restoration and weight
1263 maintenance in women with anorexia nervosa. *Am J Clin Nutr* 2009: **90**; 1132-1137.
1264 McCosh RB, Breen KM, and Kauffman AS. Neural and endocrine mechanisms underlying stress-
1265 induced suppression of pulsatile LH secretion. *Mol Cell Endocrinol* 2019: **498**; 110579.
1266 Mecklenburg RS, Loriaux DL, Thompson RH, Andersen AE, and Lipsett MB. Hypothalamic
1267 dysfunction in patients with anorexia nervosa. *Medicine (Baltimore)* 1974: **53**; 147-159.
1268 Meczekalski B, Podfigurna-Stopa A, Warenik-Szymankiewicz A, and Genazzani AR. Functional
1269 hypothalamic amenorrhea: current view on neuroendocrine aberrations. *Gynecol*
1270 *Endocrinol* 2008: **24**; 4-11.
1271 Melin A, Tornberg AB, Skouby S, Moller SS, Faber J, Sundgot-Borgen J, and Sjodin A. Low-energy
1272 density and high fiber intake are dietary concerns in female endurance athletes. *Scand J*
1273 *Med Sci Sports* 2016: **26**; 1060-1071.
1274 Mello NK. Effects of alcohol abuse on reproductive function in women. *Recent Dev Alcohol*
1275 1988: **6**; 253-276.
1276 Mendelson T. Stress, Emotional. In Gellman, MD and Turner, JR (eds) Encyclopedia of
1277 Behavioral Medicine. 2013. Springer New York, New York, NY, pp 1906-1908.
1278 Michopoulos V, Berga SL, Kaplan JR, and Wilson ME. Social subordination and polymorphisms in
1279 the gene encoding the serotonin transporter enhance estradiol inhibition of luteinizing
1280 hormone secretion in female rhesus monkeys. *Biol Reprod* 2009: **81**; 1154-1163.
1281 Michopoulos V, Mancini F, Loucks TL, and Berga SL. Neuroendocrine recovery initiated by
1282 cognitive behavioral therapy in women with functional hypothalamic amenorrhea: a
1283 randomized, controlled trial. *Fertil Steril* 2013: **99**; 2084-2091.e2081.
1284 Miller KK, Grinspoon S, Gleysteen S, Grieco KA, Ciampa J, Breu J, Herzog DB, and Klibanski A.
1285 Preservation of neuroendocrine control of reproductive function despite severe
1286 undernutrition. *J Clin Endocrinol Metab* 2004: **89**; 4434-4438.
1287 Miller KK, Parulekar MS, Schoenfeld E, Anderson E, Hubbard J, Klibanski A, and Grinspoon SK.
1288 Decreased leptin levels in normal weight women with hypothalamic amenorrhea: the
1289 effects of body composition and nutritional intake. *J Clin Endocrinol Metab* 1998: **83**;
1290 2309-2312.
1291 Misra M, Prabhakaran R, Miller KK, Tsai P, Lin A, Lee N, Herzog DB, and Klibanski A. Role of
1292 cortisol in menstrual recovery in adolescent girls with anorexia nervosa. *Pediatr Res*
1293 2006: **59**; 598-603.
1294 Mountjoy M, Sundgot-Borgen JK, Burke LM, Ackerman KE, Blauwet C, Constantini N, Lebrun C,
1295 Lundy B, Melin AK, Meyer NL*, et al.* IOC consensus statement on relative energy
1296 deficiency in sport (RED-S): 2018 update. *Br J Sports Med* 2018: **52**; 687.
1297 Murahashi K, Bucholtz DC, Nagatani S, Tsukahara S, Tsukamura H, Foster DL, and Maeda KI.
1298 Suppression of luteinizing hormone pulses by restriction of glucose availability is
1299 mediated by sensors in the brain stem. *Endocrinology* 1996: **137**; 1171-1176.
1300 Nakamura A, Osonoi T, and Terauchi Y. Relationship between urinary sodium excretion and
1301 pioglitazone-induced edema. *J Diabetes Investig* 2010: **1**; 208-211.
1302 Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, and Warren MP. American
1303 College of Sports Medicine position stand. The female athlete triad. *Med Sci Sports*
1304 *Exerc* 2007: **39**; 1867-1882.

Navarro VM and Kaiser UB. Metabolic influences on neuroendocrine regulation of reproduction. *Curr Opin Endocrinol Diabetes Obes* 2013: **20**; 335-341.
Neuberg M, Pawlosek W, Jakubowska-Szwed B, Waciega A, and Turkiewicz M. [Repeated amenorrhea in an adolescent girl in the course of flood disaster in Klodzko Region, July 1997]. *Ginekol Pol* 1999: **70**; 378-382.
Olster DH and Ferin M. Corticotropin-releasing hormone inhibits gonadotropin secretion in the ovariectomized rhesus monkey. *J Clin Endocrinol Metab* 1987: **65**; 262-267.
Palm-Fischbacher S and Ehlert U. Dispositional resilience as a moderator of the relationship between chronic stress and irregular menstrual cycle. *J Psychosom Obstet Gynaecol* 2014: **35**; 42-50.
Pauli SA and Berga SL. Athletic amenorrhea: energy deficit or psychogenic challenge? *Ann N Y Acad Sci* 2010: **1205**; 33-38.
Pentz I and Nakic Rados S. Functional hypothalamic amenorrhea and its psychological correlates: a controlled comparison. *J Reprod Infant Psychol* 2017: **35**; 137-149.
Peric M, Zenic N, Sekulic D, Kondric M, and Zaletel P. Disordered eating, amenorrhea, and substance use and misuse among professional ballet dancers: Preliminary analysis. *Med Pr* 2016: **67**; 21-27.
Petraglia F, Sutton S, Vale W, and Plotsky P. Corticotropin-releasing factor decreases plasma luteinizing hormone levels in female rats by inhibiting gonadotropin-releasing hormone release into hypophysial-portal circulation. *Endocrinology* 1987: **120**; 1083-1088.
Pirke KM, Schweiger U, Strowitzki T, Tuschl RJ, Laessle RG, Broocks A, Huber B, and Middendorf R. Dieting causes menstrual irregularities in normal weight young women through impairment of episodic luteinizing hormone secretion. *Fertil Steril* 1989: **51**; 263-268.
Pitts S, Blood E, Divasta A, and Gordon CM. Percentage body fat by dual-energy X-ray absorptiometry is associated with menstrual recovery in adolescents with anorexia nervosa. *J Adolesc Health* 2014: **54**; 739-741.
Plant TM. The neurobiological mechanism underlying hypothalamic GnRH pulse generation: the role of kisspeptin neurons in the arcuate nucleus. *F1000Res* 2019: **8**.
Qiu X, Dowling AR, Marino JS, Faulkner LD, Bryant B, Bruning JC, Elias CF, and Hill JW. Delayed puberty but normal fertility in mice with selective deletion of insulin receptors from Kiss1 cells. *Endocrinology* 2013: **154**; 1337-1348.
Quigley ME, Sheehan KL, Casper RF, and Yen SS. Evidence for increased dopaminergic and opioid activity in patients with hypothalamic hypogonadotropic amenorrhea. *J Clin Endocrinol Metab* 1980: **50**; 949-954.
Raftogianni A, Roth LC, Garcia-Gonzalez D, Bus T, Kuhne C, Monyer H, Spergel DJ, Deussing JM, and Grinevich V. Deciphering the Contributions of CRH Receptors in the Brain and Pituitary to Stress-Induced Inhibition of the Reproductive Axis. *Front Mol Neurosci* 2018: **11**; 305.
Ralph CR, Lehman MN, Goodman RL, and Tilbrook AJ. Impact of psychosocial stress on gonadotrophins and sexual behaviour in females: role for cortisol? *Reproduction* 2016: **152**; R1-r14.
Rani K, Tiwari SC, Singh U, Agrawal GG, and Srivastava N. Six-month trial of Yoga Nidra in menstrual disorder patients: Effects on somatoform symptoms. *Industrial psychiatry journal* 2011: **20**; 97-102.
Rasky E, Stronegger WJ, and Freidl W. The relationship between body weight and patterns of smoking in women and men. *Int J Epidemiol* 1996: **25**; 1208-1212.

Reed JL, De Souza MJ, Mallinson RJ, Scheid JL, and Williams NI. Energy availability discriminates clinical menstrual status in exercising women. *J Int Soc Sports Nutr* 2015: **12**; 11.

Remorgida V, Venturini PL, Anserini P, Salerno E, and De Cecco L. Naltrexone in functional hypothalamic amenorrhea and in the normal luteal phase. *Obstet Gynecol* 1990: **76**; 1115-1120.

Rettberg JR, Yao J, and Brinton RD. Estrogen: a master regulator of bioenergetic systems in the brain and body. *Front Neuroendocrinol* 2014: **35**; 8-30.

Richards JS, Ireland JJ, Rao MC, Bernath GA, Midgley AR, Jr., and Reichert LE, Jr. Ovarian follicular development in the rat: hormone receptor regulation by estradiol, follicle stimulating hormone and luteinizing hormone. *Endocrinology* 1976: **99**; 1562-1570.

Rigaud D, Pennacchio H, Bizeul C, Reveillard V, and Verges B. Outcome in AN adult patients: a 13-year follow-up in 484 patients. *Diabetes Metab* 2011: **37**; 305-311.

Roa J, Garcia-Galiano D, Castellano JM, Gaytan F, Pinilla L, and Tena-Sempere M. Metabolic control of puberty onset: new players, new mechanisms. *Mol Cell Endocrinol* 2010: **324**; 87-94.

Roland AV and Moenter SM. Regulation of gonadotropin-releasing hormone neurons by glucose. *Trends Endocrinol Metab* 2011: **22**; 443-449.

Ronnekleiv OK, Qiu J, and Kelly MJ. Arcuate Kisspeptin Neurons Coordinate Reproductive Activities with Metabolism. *Semin Reprod Med* 2019: **37**; 131-140.

Roupas ND and Georgopoulos NA. Menstrual function in sports. *Hormones (Athens)* 2011: **10**; 104-116.

Ruiz-Cortes ZT, Martel-Kennes Y, Gevry NY, Downey BR, Palin MF, and Murphy BD. Biphasic effects of leptin in porcine granulosa cells. *Biol Reprod* 2003: **68**; 789-796.

Saketos M, Sharma N, and Santoro NF. Suppression of the hypothalamic-pituitary-ovarian axis in normal women by glucocorticoids. *Biol Reprod* 1993: **49**; 1270-1276.

Sanborn CF, Martin BJ, and Wagner WW, Jr. Is athletic amenorrhea specific to runners? *Am J Obstet Gynecol* 1982: **143**; 859-861.

Sanchez-Garrido MA and Tena-Sempere M. Metabolic control of puberty: roles of leptin and kisspeptins. *Horm Behav* 2013: **64**; 187-194.

Sanders KA and Bruce NW. Psychosocial stress and the menstrual cycle. *J Biosoc Sci* 1999: **31**; 393-402.

Sawyer CH. First Geoffrey Harris Memorial Lecture. Some Recent Developments in Brain-Pituitary-Ovarian Physiology. *Neuroendocrinology* 1975: **17**; 97-124.

Schedlowski M, Wiechert D, Wagner TOF, and Tewes U. Acute psychological stress increases plasma levels of cortisol, prolactin and TSH. *Life Sciences* 1992: **50**; 1201-1205.

Schliep KC, Zarek SM, Schisterman EF, Wactawski-Wende J, Trevisan M, Sjaarda LA, Perkins NJ, and Mumford SL. Alcohol intake, reproductive hormones, and menstrual cycle function: a prospective cohort study. *Am J Clin Nutr* 2015: **102**; 933-942.

Schneider LF, Monaco SE, and Warren MP. Elevated ghrelin level in women of normal weight with amenorrhea is related to disordered eating. *Fertil Steril* 2008: **90**; 121-128.

Shanan J, Brzezinski A, Sulman F, and Sharon M. Active coping behavior, anxiety, and cortical steroid excretion in the prediction of transient amenorrhea. *Behav Sci* 1965: **10**; 461-465.

Shen ZQ, Xu JJ, and Lin JF. Resumption of menstruation and pituitary response to gonadotropin-releasing hormone in functional hypothalamic amenorrhea subjects undertaking estrogen replacement therapy. *J Endocrinol Invest* 2013: **36**; 812-815.

Shilaih M, Clerck V, Falco L, Kubler F, and Leeners B. Pulse Rate Measurement During Sleep Using Wearable Sensors, and its Correlation with the Menstrual Cycle Phases, A Prospective Observational Study. *Sci Rep* 2017: **7**; 1294.

Smith AR, Ortiz SN, Forrest LN, Velkoff EA, and Dodd DR. Which Comes First? An Examination of Associations and Shared Risk Factors for Eating Disorders and Suicidality. *Curr Psychiatry Rep* 2018: **20**; 77.

Sobrinho LG. Prolactin, psychological stress and environment in humans: adaptation and maladaptation. *Pituitary* 2003: **6**; 35-39.

Somigliana E, Paffoni A, Busnelli A, Filippi F, Pagliardini L, Vigano P, and Vercellini P. Age-related infertility and unexplained infertility: an intricate clinical dilemma. *Human Reproduction* 2016: **31**; 1390-1396.

Sominsky L, Hodgson DM, McLaughlin EA, Smith R, Wall HM, and Spencer SJ. Linking Stress and Infertility: A Novel Role for Ghrelin. *Endocr Rev* 2017: **38**; 432-467.

Sonigo C, Bouilly J, Carre N, Tolle V, Caraty A, Tello J, Simony-Conesa FJ, Millar R, Young J, and Binart N. Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration. *J Clin Invest* 2012: **122**; 3791-3795.

Sonino N, Navarrini C, Ruini C, Fallo F, Boscaro M, and Fava GA. Life events in the pathogenesis of hyperprolactinemia. *Eur J Endocrinol* 2004: **151**; 61-65.

Sowinska-Przepiera E, Andrysiak-Mamos E, Jarzabek-Bielecka G, Walkowiak A, Osowicz-Korolonek L, Syrenicz M, Kedzia W, and Syrenicz A. Functional hypothalamic amenorrhoea - diagnostic challenges, monitoring, and treatment. *Endokrynol Pol* 2015: **66**; 252-260.

Sterling WM, Golden NH, Jacobson MS, Ornstein RM, and Hertz SM. Metabolic assessment of menstruating and nonmenstruating normal weight adolescents. *Int J Eat Disord* 2009: **42**; 658-663.

Suh BY, Liu JH, Berga SL, Quigley ME, Laughlin GA, and Yen SS. Hypercortisolism in patients with functional hypothalamic-amenorrhea. *J Clin Endocrinol Metab* 1988: **66**; 733-739.

Sun Y, Ahmed S, and Smith RG. Deletion of ghrelin impairs neither growth nor appetite. *Mol Cell Biol* 2003: **23**; 7973-7981.

Sun Y, Butte NF, Garcia JM, and Smith RG. Characterization of adult ghrelin and ghrelin receptor knockout mice under positive and negative energy balance. *Endocrinology* 2008: **149**; 843-850.

Swenne I. Weight requirements for return of menstruations in teenage girls with eating disorders, weight loss and secondary amenorrhoea. *Acta Paediatr* 2004: **93**; 1449-1455.

Sydenham A. Amenorrhoea at Stanley Camp, Hong Kong, during internment. *Br Med J* 1946: **2**; 159.

Szymanski LA, Schneider JE, Friedman MI, Ji H, Kurose Y, Blache D, Rao A, Dunshea FR, and Clarke IJ. Changes in insulin, glucose and ketone bodies, but not leptin or body fat content precede restoration of luteinising hormone secretion in ewes. *J Neuroendocrinol* 2007: **19**; 449-460.

Tena-Sempere M. Roles of ghrelin and leptin in the control of reproductive function. *Neuroendocrinology* 2007: **86**; 229-241.

Tena-Sempere M. Interaction between energy homeostasis and reproduction: central effects of leptin and ghrelin on the reproductive axis. *Horm Metab Res* 2013: **45**; 919-927.

Theorell T. Prolactin-a hormone that mirrors passiveness in crisis situations. *Integrative Physiological and Behavioral Science* 1992: **27**; 32-38.

1443 Tinahones FJ, Martinez-Alfaro B, Gonzalo-Marin M, Garcia-Almeida JM, Garrido-Sanchez L, and
1444 Cardona F. Recovery of menstrual cycle after therapy for anorexia nervosa. *Eat Weight*
1445 *Disord* 2005: **10**; e52-55.
1446 Tokatly Latzer I, Kidron-Levy H, Stein D, Levy AE, Yosef G, Ziv-Baran T, and Dubnov-Raz G.
1447 Predicting Menstrual Recovery in Adolescents With Anorexia Nervosa Using Body Fat
1448 Percent Estimated by Bioimpedance Analysis. *J Adolesc Health* 2019: **64**; 454-460.
1449 Tolle V, Kadem M, Bluet-Pajot MT, Frere D, Foulon C, Bossu C, Dardennes R, Mounier C, Zizzari
1450 P, Lang F*, et al.* Balance in ghrelin and leptin plasma levels in anorexia nervosa patients
1451 and constitutionally thin women. *J Clin Endocrinol Metab* 2003: **88**; 109-116.
1452 Tschugguel W and Berga SL. Treatment of functional hypothalamic amenorrhea with
1453 hypnotherapy. *Fertil Steril* 2003: **80**; 982-985.
1454 Turzillo AM, Nolan TE, and Nett TM. Regulation of gonadotropin-releasing hormone (GnRH)
1455 receptor gene expression in sheep: interaction of GnRH and estradiol. *Endocrinology*
1456 1998: **139**; 4890-4894.
1457 Vazquez MJ, Velasco I, and Tena-Sempere M. Novel mechanisms for the metabolic control of
1458 puberty: implications for pubertal alterations in early-onset obesity and malnutrition. *J*
1459 *Endocrinol* 2019: **242**; R51-r65.
1460 Villanueva AL, Schlosser C, Hopper B, Liu JH, Hoffman DI, and Rebar RW. Increased cortisol
1461 production in women runners. *J Clin Endocrinol Metab* 1986: **63**; 133-136.
1462 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, and Vandenbroucke JP. The
1463 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
1464 statement: guidelines for reporting observational studies. *Lancet* 2007: **370**; 1453-1457.
1465 Voorhuis M, Onland-Moret NC, van der Schouw YT, Fauser BC, and Broekmans FJ. Human
1466 studies on genetics of the age at natural menopause: a systematic review. *Hum Reprod*
1467 *Update* 2010: **16**; 364-377.
1468 Wade GN and Jones JE. Neuroendocrinology of nutritional infertility. *Am J Physiol Regul Integr*
1469 *Comp Physiol* 2004: **287**; R1277-1296.
1470 Wagenmaker ER, Breen KM, Oakley AE, Tilbrook AJ, and Karsch FJ. Psychosocial stress inhibits
1471 amplitude of gonadotropin-releasing hormone pulses independent of cortisol action on
1472 the type II glucocorticoid receptor. *Endocrinology* 2009: **150**; 762-769.
1473 Walf AA and Frye CA. A review and update of mechanisms of estrogen in the hippocampus and
1474 amygdala for anxiety and depression behavior. *Neuropsychopharmacology* 2006: **31**;
1475 1097-1111.
1476 Warren MP. The effects of exercise on pubertal progression and reproductive function in girls. *J*
1477 *Clin Endocrinol Metab* 1980: **51**; 1150-1157.
1478 Warren MP and Perlroth NE. The effects of intense exercise on the female reproductive system.
1479 *J Endocrinol* 2001: **170**; 3-11.
1480 Warren MP, Voussoughian F, Geer EB, Hyle EP, Adberg CL, and Ramos RH. Functional
1481 hypothalamic amenorrhea: hypoleptinemia and disordered eating. *J Clin Endocrinol*
1482 *Metab* 1999: **84**; 873-877.
1483 Watson TL and Andersen AE. A critical examination of the amenorrhea and weight criteria for
1484 diagnosing anorexia nervosa. *Acta Psychiatr Scand* 2003: **108**; 175-182.
1485 Weber RF and Calogero AE. Prolactin stimulates rat hypothalamic corticotropin-releasing
1486 hormone and pituitary adrenocorticotropin secretion in vitro. *Neuroendocrinology*
1487 1991: **54**; 248-253.
1488 Weisberg E. Smoking and reproductive health. *Clin Reprod Fertil* 1985: **3**; 175-186.

Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, Karalis A, and Mantzoros CS. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* 2004: **351**; 987-997.

Wildt L and Leyendecker G. Induction of ovulation by the chronic administration of naltrexone in hypothalamic amenorrhea. *J Clin Endocrinol Metab* 1987: **64**; 1334-1335.

Wildt L, Leyendecker G, Sir-Petermann T, and Waibel-Treber S. Treatment with naltrexone in hypothalamic ovarian failure: induction of ovulation and pregnancy. *Hum Reprod* 1993: **8**; 350-358.

William Tank A and Lee Wong D. Peripheral and Central Effects of Circulating Catecholamines. Comprehensive Physiology. 2014. pp 1-15.

Williams NI, Berga SL, and Cameron JL. Synergism between psychosocial and metabolic stressors: impact on reproductive function in cynomolgus monkeys. *Am J Physiol Endocrinol Metab* 2007: **293**; E270-276.

Williams NI, Helmreich DL, Parfitt DB, Caston-Balderrama A, and Cameron JL. Evidence for a causal role of low energy availability in the induction of menstrual cycle disturbances during strenuous exercise training. *J Clin Endocrinol Metab* 2001: **86**; 5184-5193.

Williams NI, Leidy HJ, Hill BR, Lieberman JL, Legro RS, and De Souza MJ. Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction. *Am J Physiol Endocrinol Metab* 2015: **308**; E29-E39.

Winkler LA, Frolich JS, Schulpen M, and Stoving RK. Body composition and menstrual status in adults with a history of anorexia nervosa-at what fat percentage is the menstrual cycle restored? *Int J Eat Disord* 2017: **50**; 370-377.

Wong SL, DePaoli AM, Lee JH, and Mantzoros CS. Leptin hormonal kinetics in the fed state: effects of adiposity, age, and gender on endogenous leptin production and clearance rates. *J Clin Endocrinol Metab* 2004: **89**; 2672-2677.

Wu S, Divall S, Wondisford F, and Wolfe A. Reproductive tissues maintain insulin sensitivity in diet-induced obesity. *Diabetes* 2012: **61**; 114-123.

Zuure WA, Roberts AL, Quennell JH, and Anderson GM. Leptin signaling in GABA neurons, but not glutamate neurons, is required for reproductive function. *J Neurosci* 2013: **33**; 17874-17883.